EVALUATION OF HOMOCYSTEINE AND FOLIC ACID LEVELS IN PREGNANCY LOSS

A Dissertation Submitted to

THE TAMILNADU DR. M.G.R MEDICAL

UNIVERSITY, CHENNAI

In Partial Fulfilment of the Regulations for

the Award of the Degree of

M.S. (OBSTETRICS & GYNAECOLOGY) - BRANCH – II

GOVERNMENT STANLEY MEDICALCOLLEGECHENNAI

April –2016

BONAFIDECERTIFICATE

This is to certify that this dissertation is a bonafide work of **Dr.SOWGANTHIKA .N.I** on **''EVALUATION OF HOMOCYSTEINE AND FOLIC ACID LEVELS IN PREGNANCY LOSS"** during her M.S., (Obstetrics and Gynaecology) course from July 2013 to July 2016 at the Government Stanley Medical College and Government Raja Sir Ramasamy Mudaliar Lying-in Hospital, Chennai.

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DECLARATION

I, Dr. SOWGANTHIKA .N.I. Solemnly declare that the dissertation **''EVALUATION OF HOMOCYSTEINE AND FOLIC ACID LEVELS IN PREGNANCY LOSS"** is a bonafide work done by me at Government R.S.R.M Lying in Hospital, under supervision and guidance of **Associate Prof. Dr. K. KALAIVANI, M.D.,DGO** in Department of Obstetrics and Gynaecology, Government Stanley Medical College, Chennai. This thesis is submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfilment of the rules and regulations for the M.S. Degree examinations in Obstetrics and Gynaecology to be held in April 2016.

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ACKNOWLEDGEMENT

I gratefully acknowledge and sincerely thank **Prof. DR.ISAAC CHRISTIAN MOSES MD FICP FACP** DEAN**,** Stanley Medical College and Govt. RSRM Lying in Hospital, Chennai 600001 for permitting me to conduct the study and use the facilities of the Institution for my study.

I am extremely thankful to the Professor and Head of the Department, **Prof. DR. P.VASANTHAMANI, M.D., DGO, Govt**. RSRM Lying in Hospital, Chennai, for her support in conducting this study.

I wish to express my deep sense of gratitude to my Guide and Associate Professor **Dr. K. KALAIVANI,** MD., DGO**,** for her valuable guidance and supervision throughout my study.

I am thankful to my Co-Guide Dr. **S. LAVANYA, M.D O.G.,** for her valuable guidance and precise suggestions at every stage of this study.

I am thankful to the RMO and all UNIT CHIEFS for their support, advice and encouragement.

I am thankful to all Assistant Professors for their guidance and help.

I thank my family members for their constant encouragement and moral support throughout this study.

Last, but not the least, I thank all my patients for their kind co-operation who made this study feasible.

CONTENTS

EVALUATION OF HOMOCYSTEINE AND FOLIC ACID LEVELS IN PREGNANCY LOSS

ABSTRACT

STUDY PERIOD

The period of study was from JANUARY 2015 – DECEMBER 2015

STUDY DESIGN

Observational study

METHODOLOGY

- Study population includes patients with pregnancy loss within 13 weeks of menstrual age
- To measure fasting homo cysteine & folic acid levels

INCLUSION CRITERIA

CASES –

- In my study 100 Patients with pregnancy loss within 13 weeks of menstrual age

CONTROLS –100 controls chosen

- Patients attending ante natal outpatient department who had at least one live child with no history of previous abortions.

EXCLUSION CRITERIA

Patients with

- Increased serum creatinine
- Increased serum alanine amino transferase
- Ectopic pregnancy
- Molar pregnancy
- Chronic hyper tension
- Diabetes mellitus
- Preexisting liver or renal disorder
- History of thromboembolism
- Abruptio placenta
- Pre term labour
- Anemia
- Smoking
- B12 & folic acid supplementation

All pregnancies to be confirmed by a positive urinary hCG test or ultrasound imaging.

• Fasting Blood sample taken after obtaining consent from the Patient

CONCLUSION → INCREASED homocystine and DECREASED folic acid level in patients with pregnancy loss & treating patients with FOLIC ACID & Multi VIT tablets. In my study out of 100 cases 21 patient where with increased homocystine and 41 patients with decreased folic acid level and therapeutic dosage of folic acid given. This study shows p value less than .001 which is highly significant.

Thus I conclude evaluation of homocystine and folic acid levels can be a marker for prediction for pregnancy in future.

• Pedigree analysis of the patients done detail

KEYWORDS :

- Homocystine
- Folic acid
- Pregnancy Loss

INTRODUCTION

- Recurrent pregnancy loss affects 1 in 300 and 1 in 100 couples

- Parenteral chromosomal abnormalities and anti-phospholipid antibody syndrome are the undisputed causes of pregnancy loss.

The pathogenesis of spontaneous abortion involves interaction of several genetic and environmental factors. Increased homocysteine concentration leads to neural tube defects (NTD) and also hyper homocysteinemia is embryotoxic and lead to decreased fetal viability.

Defects in Folate- and vitamin B12-dependent homocysteine metabolism are linked with genetic polymorphism (Henrik Zetterberg et al) Transmethylation of methionine leads to formation of homocysteine and its metabolism depends primarily on four enzymes – methyl tetra hydro folate reductase, cysta thionine beta synthase, methionine synthase, acetyl choline transferase and several vitamin cofactors.

Fasting value 15 micro mol/l - cut off value for hyperhomocystenemia HHCh belongs among the congenital hypercoagulable states and is a long-known vascular disease risk

factor. HHCh is responsible for several pregnancy complications such as

1. Early pregnancy loss
2. Pre eclampsia
3. Abruption
4. Intra uterine death
5. Still births
6. Neural tube defects
7. Growth restriction
8. Thromboembolic episodes

Anticoagulant treatment –the treatment for thromboembolic episodes during pregnancy(Aubard Y etal.,2000) Folates belong to the vitamin B group and are involved in a large number of biochemical processes, particularly in the metabolism of homocysteine. Any research in this field would prove immense help to patients with recurrent miscarriage as well help them in preventing future complications not only of pregnancy but also in preventing coronary artery disease, dementia, osteoporosis, lack of concentration and underachievement for which they are more prone. It is shown by studies that women with recurrent miscarriage were more likely to

have family history of cardiovascular disease (GCS Smith, AM Wood, JP Pell, J Hattie)[2]

Other causes are:

- Anatomic
- Endocrine
- Thrombotic
- Immunologic factors.

- Altered balance between pro-thrombotic and antithrombotic factors.
- Evaluation by detailed family history and patient history, focused mainly on endocrine and anatomical abnormalities.
- Early pregnancy loss monitored by a)USG b) beta- HCG c) Karyotype analysis.

Treatment of Recurrent pregnancy loss:

- Correction of anatomic abnormalities
- Correcting preexisting endocrine disorders
- Antiphospholipid antibody syndrome and thrombophilic disorders to be treated.

Incidence of Pregnancy loss 15% - clinically recognized before 20 weeks from last menstrual period.

Risk of subsequent pregnancy loss in previous history of recurrent pregnancy losses 24% after 2 losses, 30% after 3 losses, 40% – 50% after 4 losses 70% of human conceptions fail to achieve viability, 50% are lost before the first missed menstrual period.

AIMS & OBJECTIVES

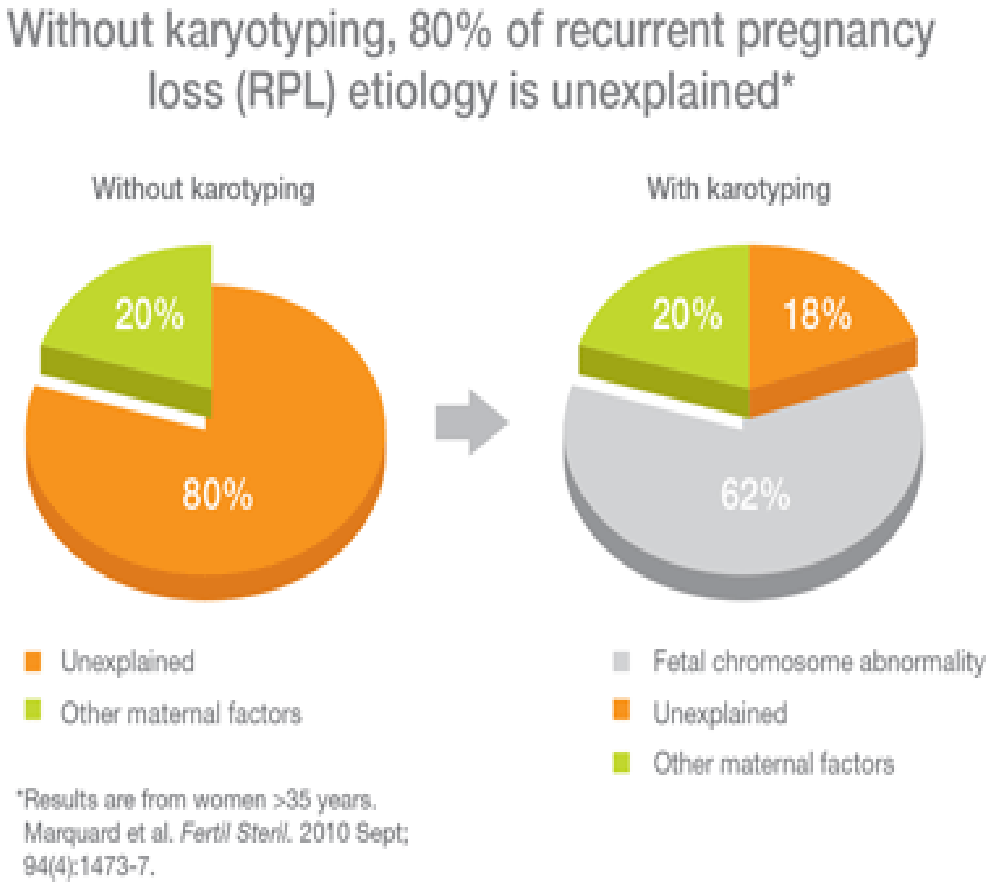
- To evaluate homocysteine & folic acid levels in pregnancy loss within 13 weeks of menstrual age.

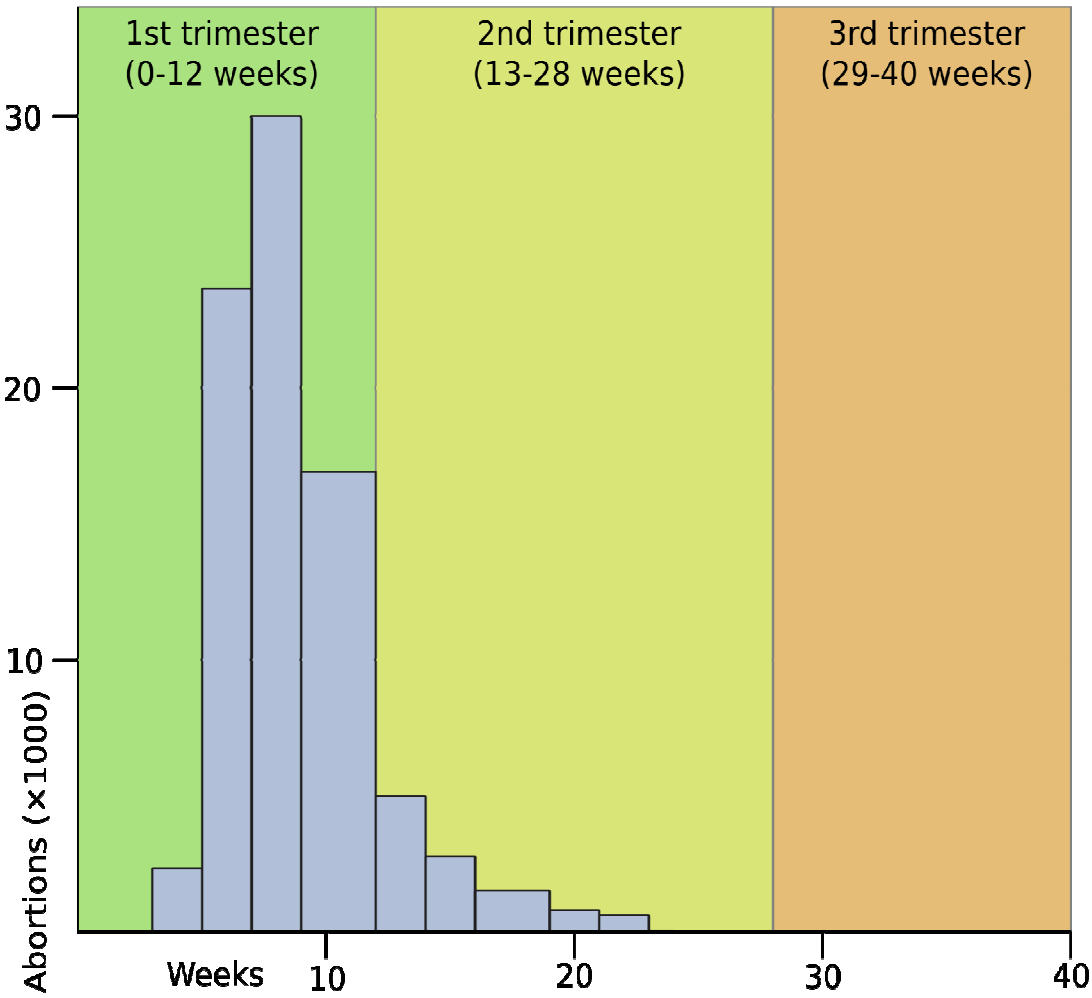
- 100 cases and 100 controls in selection criteria

- Treating patients with folic acid and multi vitamin tablets with elevated homocysteine levels and decreased folic acid levels

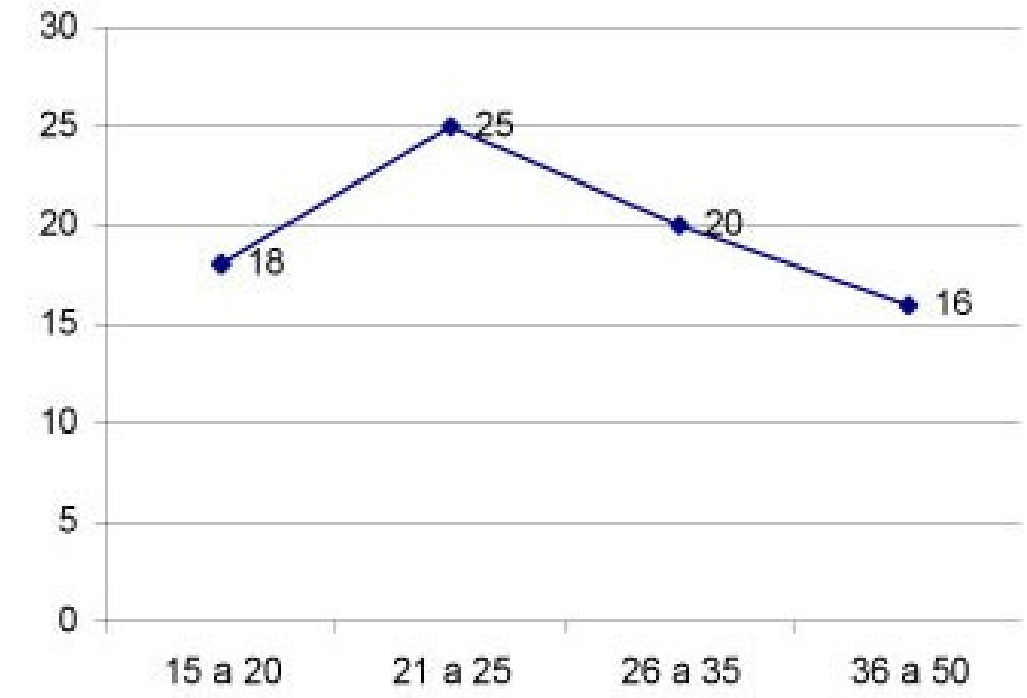
REVIEW OF LITERATURE

The term miscarriage is used to define a pregnancy that fails to progress , resulting in death and expulsion of a embryo ≤ 500 gms equal to 20 weeks of pregnancy. Spontaneous miscarriage is the commonest complication of pregnancy. It occurs in up to 20% of clinical pregnancies(Poulose et al).




1st trimester
(0-12 weeks)
2nd trimester
(13-28 weeks)
3rd trimester
(29-40 weeks)
30
20
10
Abortions (×1000)
Weeks
10
20
30
40

AGE RELATED MISCARRIAGES



ETIOLOGIES FOR RECURRENT SPONTANEOUS ABORTION

ETIOLOGY	INCIDENCE
A. Genetic factors	3.5% - 5%
1. Chromosomal	
2. Single gene defects	
3. Multifactorial	
B. Anatomic factors	12% - 16%
1. Congenital	
a. incomplete mullerian fusion or septum resorption	
b. Diethylstilbestrol exposure	
c. uterine artery manomalies	
d. cervical incompetence	

2. Acquired

a. cervical incompetence

b. synechiae

c. leiomyomas

d. adenomyosis

C. Endocrine factors 17% - 20%

1. luteal phase insufficiency

2. Polycystic ovarian syndrome, including insulin resistance and hyperandrogenism

3. Other androgen disorders

4. Diabetes mellitus

5. Thyroid disorders

6. Prolactin disorders

D. Infectious factors 0.5% - 5%

1. Bacteris

2. Viruses

3. Parasites

4. Zoonotic

5. Fungal

E. Immunologic factors 20% - 50%

1. Cellular mechanisms

a. Suppressor cell or factor deficiency

b. Alterations in major histocompatibilityantigen expression

c. Alterations in cellular immune regulation

1. TH1 immune responses to reproductive antigens (embryo or trophoblast)

2. Th2 cytokine or growth factor deficiency

3. Hormonal – progesterone, estrogen, prolactin, androgen alterations

4. Tryptophan metabolism

2. Humoral mechanisms

a. Antiphospholipid antibodies

b. Antithyroid antibodies

c. Antisperm antibodies

d. Antitrophoblast antibodies

e. Blocking antibody deficiency

F. Thrombotic factors incidence

1. Heritable thrombophilias

a) Single gene defects (fVL, MTHFR, factor deficiencies)

b) Antibody mediated thromboses (APS, anti – β2G1)

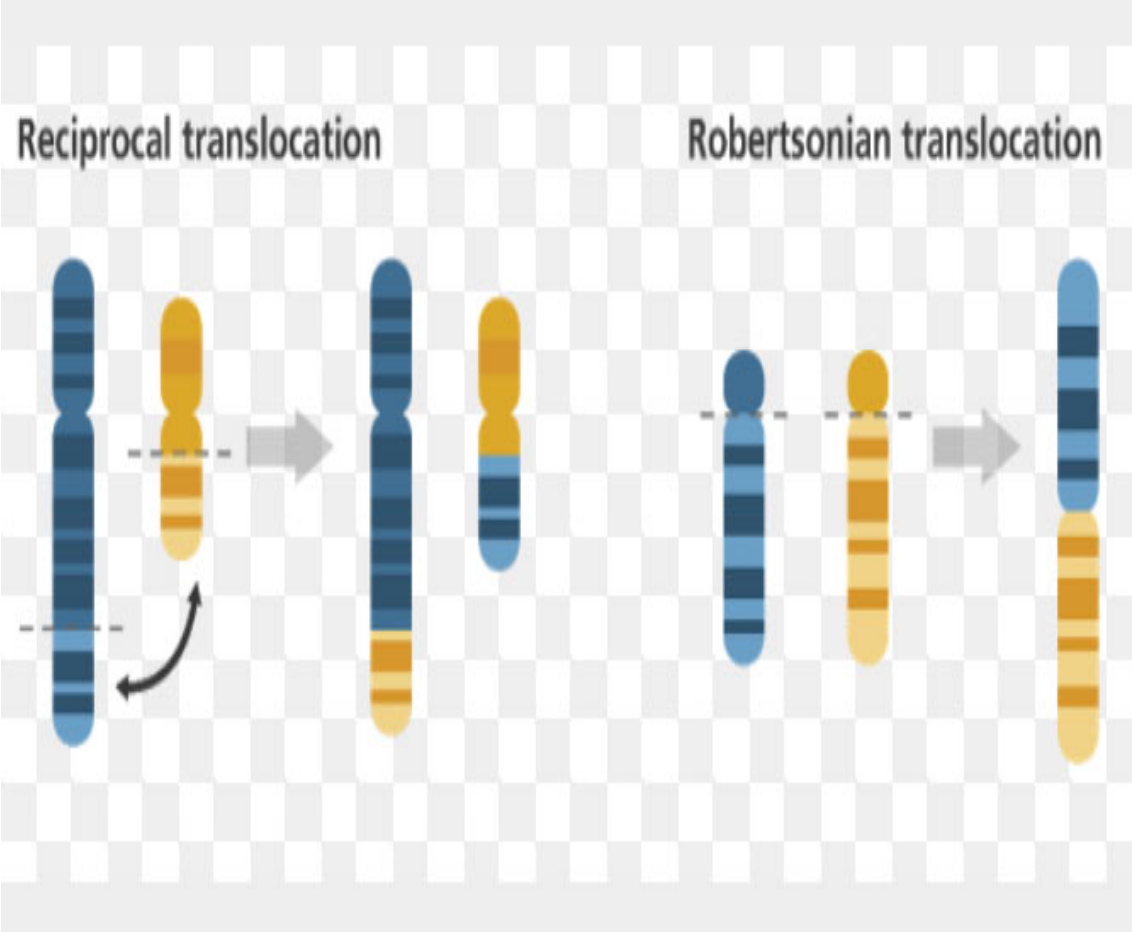
Most are included among other categories (e.g., immune, genetic)

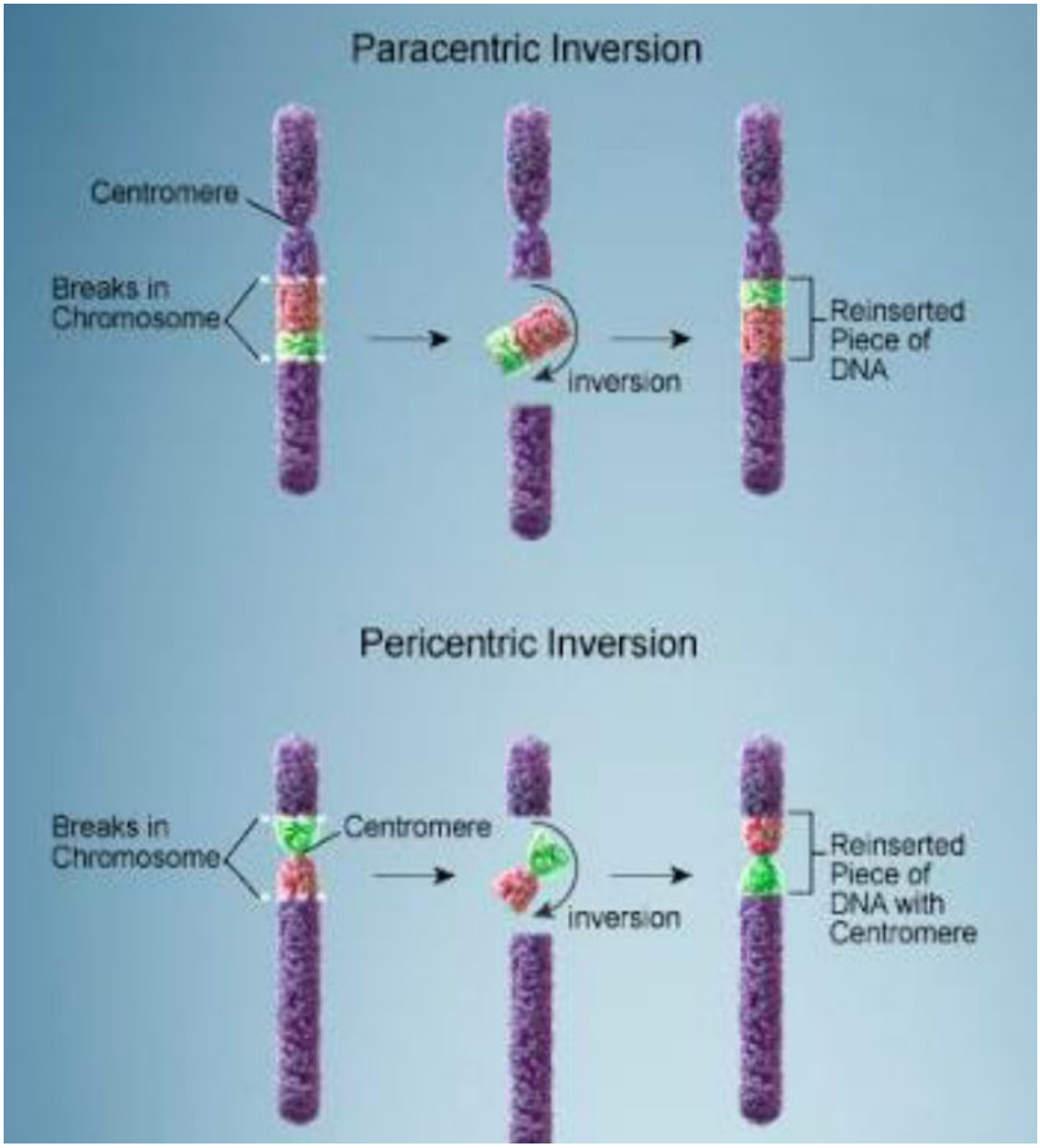
Other factors 10%

1. Altered uterine receptivity (integrins, adhesion molecules)
2. Environmental
    a) Toxins
    b) Illicit drugs
        i. Cigarettes and caffeine

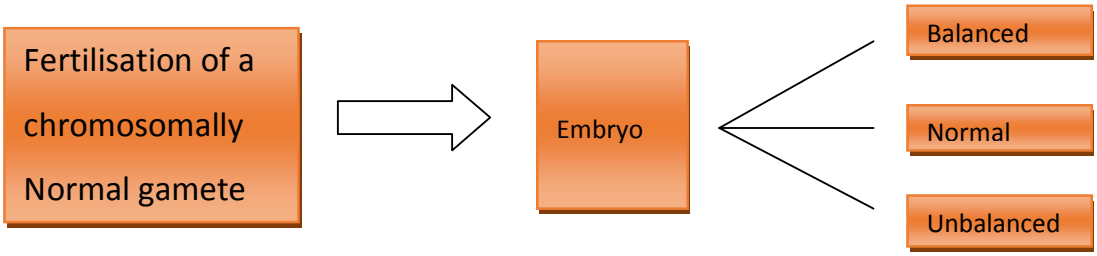
1. Placental abnormalities (circumvallate, marginate)
2. Maternal medical illnesses (cardiac, renal hematologic)
3. Male factors
4. Exercise
5. Dyssynchronous fertilization.

GENETIC FACTORS: The most common contributing to recurrent abortion are balanced translocations.




Paracentric Inversion
Centromere
Breaks in Chromosome
inversion
Reinserted Piece of DNA
Pericentric Inversion
Breaks in Chromosome
Centromere
inversion
Reinserted Piece of DNA with Centromere

Depending on the nature of the translocations gametes produced by the translocations carrier will be normal balanced or unbalanced for the translocated DNA.

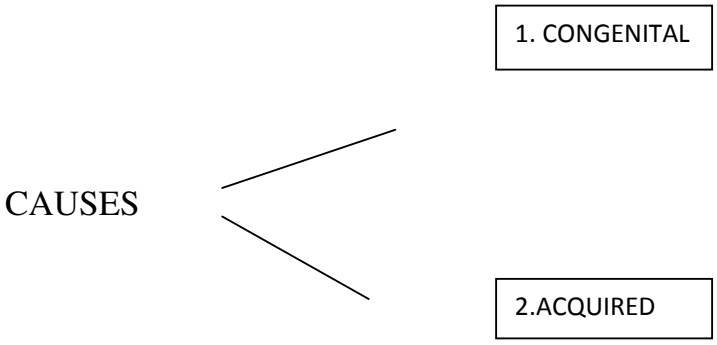


Among the possible chromosomal monosomies, X chromosome permits viable offspring. Compared with monosomies, chromosomal trisomies – 13, 18,21 appear to be better tolerated. Mosaicism may be implicated with these abnormalities.. Other structural chromosomal anomalies, such as inversions and insertions, may also contribute to recurrent abortions.

Evaluation made by use of parental karyotyping a screening modality for recurrent pregnancy loss.

ANATOMIC ABNORMALITIES

Anatomic abnormalities of both the uterine cervix and the uterine body have been associated with recurrent pregnancy loss.



Congenital causes

-incomplete mullerian duct fusion,

-incomplete septum resorption,

-uterine cervical anomalies.

-Prenatal exposure to diethyl stilbestrol

-presence of intrauterine septum

Acquired causes

-Intrauterine adhesions

-Uterine fibroids

-Endometrial polyps

ENDOCRINE ABNORMILITIES

Endocrine abnormalities mediate their effect during the follicular phasee of the cycle in which conception occurs, or even earlier. Beginning with ovulation and lasting until approximately 7 to 9 weeks of gestation, maintenance of early pregnancy depends on the production of progesterone by the corpus luteum. Normal pregnancies are characterized by a luteal-placental shift at about 7 to 9 weeks gestation during which the developing placental trophoblast cells take over progesterone production and maintains pregnancy.

Pregnancy failures may also occur near the time of the expected luteal placental shift if the trophoblast is unable to produce biologically active progesterone following corpus luteum death.

Endocrine factors associated with recurrent abortion include luteal phase insufficiency, diabetes mellitus, hypersecretion of luteinizing hormone (LH), thyroid disease, and, potentially, insulin resistance and polycystic ovarian syndrome, hyperprolactinemia and decreased ovarian reserve.

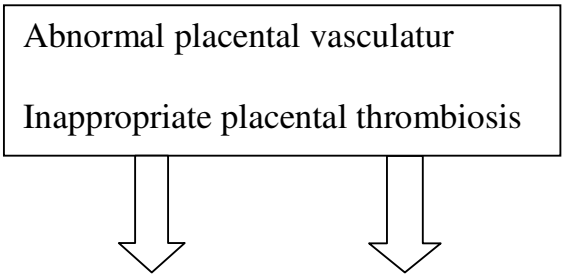
Studies report ovarian radiologic evidence of PCOS in as many as 40% to 80% of recurrent pregnancy loss patients. Many women with PCOS have metabolic alteration in glycemic control characterized by insulin resistance. This too may be directly or indirectly related to adverse pregnancy outcome, and it may explain increases in the rate of spontaneous pregnancy

loss among women with type 2 diabetes mellitus. Women with overt insulin – dependent diabetes mellitus (IDDM) appear to exibit a threshold of progestational glycemic control above which spontaneous pregnancy loss is increased . in fact, hyperglycemia has now been directly linked to embryonic damage.

In cases of advanced IDDM with accompanying vascular complications, compromised blood flow to the uterus may be mechanistically involved in subsequent pregnancy loss.

THROMBOPHILIAS:

This heterogenous group of disorders ↑ arterial/ venous thrombosis



Thrombophilic states to pregnancy loss

Heritable thrombophilias :

Linked with

- Activated protein c resistance
- Associated c factor V mutation
- Deficiencies in protein C,S

- Mutation in prothrombin
- Mutation in antithrombin III

Inherited thrombophlias

- 15% while have inheritable thrombophilia
- Factor V leiden mutation
- Mutation in promoter region of prothrombin gene & mutation in gene encoding MTHFR

More severe thrombophilias such as anti thrombin & protein S less common

IMMUNOLOGICAL FACTORS

Cellular immunity

1. Resident endometrial/decidual cells

   a. few B cells

   b. TCRαβ+ and TCRγδ+ cells increase in early pregnancy

   c. NK-like, large granular lymphocytes (decidual NK cells) accumulate at site of implantation

   d. NKT cells and suppressor macrophage

   e. Treg cells

2. immune cell education and homing

   a. thymic versus extrathymic education

   b.possible in situ education and maintenance

c.integrins/ vascular ligand and mucosal homing

3. Antigen presentation

a. MHC class II molecules are not expressed in the placenta

b. classical MHC class I molecules HLA-A and HLA-B are not expressed in the placenta

c. extravillous cytotrophoblast cells express HLA-C, HLA-E, and HLA-G

4. In situ immunoregulation

a.TH1/TH2 cytokine microenvironments and dysregulation

b. Hormonal immunomodulation

1. Progesterone

2. Estrogen

3. Human chorionic gonadotropin (hCG)

4. prolactin

5. Androgens

6. Others

c. tryptophan metabolism and indolamine 2,3 dioxygenase (IDO)

d.leukemia inhibiting factor (LIF)

Humoral Immunity

1. Fetal antigens are recognized by the maternal immune system and humoral responses are mounted.
2. Organ nonspecific autoantibodies

    a.Anticardiolipin antibodies

    b.lupus anticoagulant

    c. Anti-β2 glycoprotein-1 (anti-beta2GP-1) antibodies

    d. Antiphosphatidly serine antibodies

3. Organ specific autoantibodies

    a. Antithyroid antibodies

    b. Antisperm antibodies

    c. Antitrophoblast antibodies

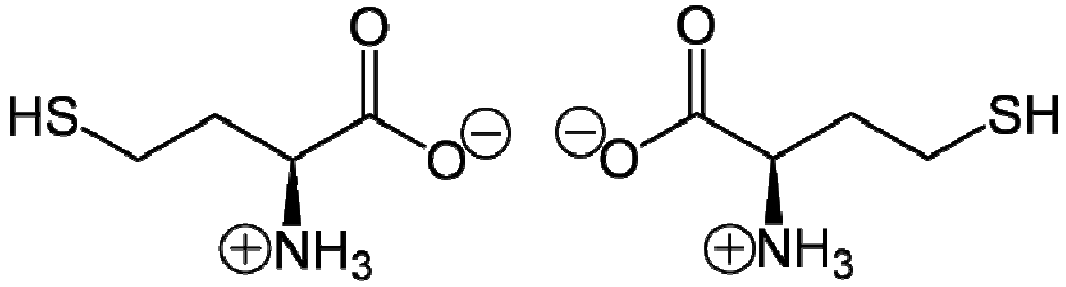
        1. blocking antibodies

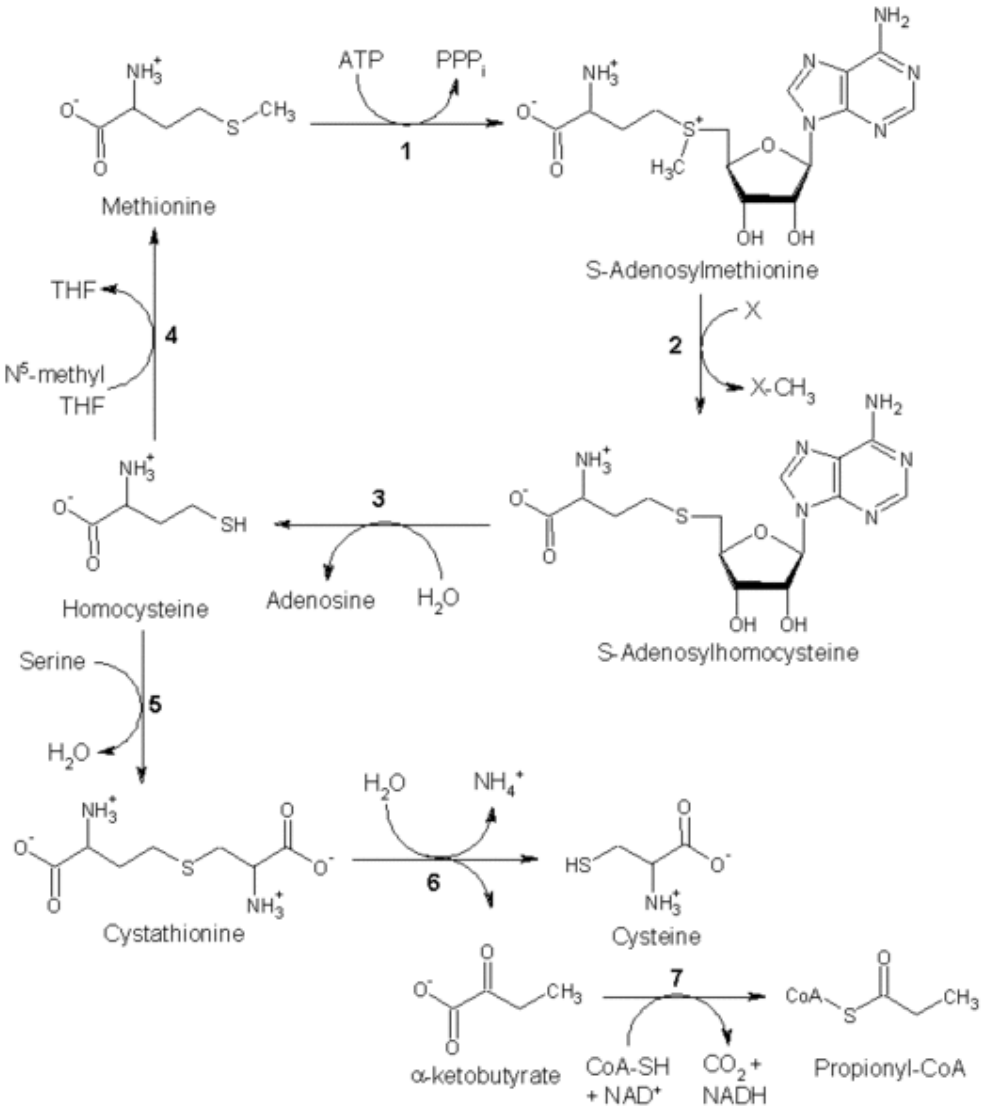
        2. HLA sharing

        3. Trophoblast/lymphocyte cross-reactive antibodies (TLX)

HOMOCYSTIENE

HOMOCYSTEINE-A thiol-containing amino acid formed by a demethylation of methionine. Hyperhomocystinemia, which may be congenital or acquired, is associated with thrombosis and premature vascular disease. This condition is also associated with pregnancy loss.





The gene for the inherited form is transmitted in an autosomal recessive form.

The most common acquired form is due to deficiency of folic acid levels.

In these patients, folic acid replacement helps achieve normal homocysteine levels within a few days.

FUNCTIONS:

- Involved in biosynthesis of DNA and RNA.
- Also via cystathionine biosynthase , cysteine is synthesized, this step uses pyridoxine as a co- factor.
- Homocystiene can be recycled to methionine , where N-5 methyl tetrahydro folate and co- balamin is used.

CAUSES OF HYPERHOMOCYSTEINE

Vitamin deficiency

-folate

-B6

-B12

- Increasing age
- Men
- Tobacco use
- Decreasing renal functions
- Enzyme deficiency

-Cystathionine β synthase

-Methionine synthase

-5 MTFHR

6-Azarudine triacetate

Homozygosity for C 6777 transition MTHFR gene

Thermolabitily of enzyme

Inhibits Formation of 5 MTHF / (methyl donor)

- Cigarette smoking
- Hypertension
- Systemic diseases

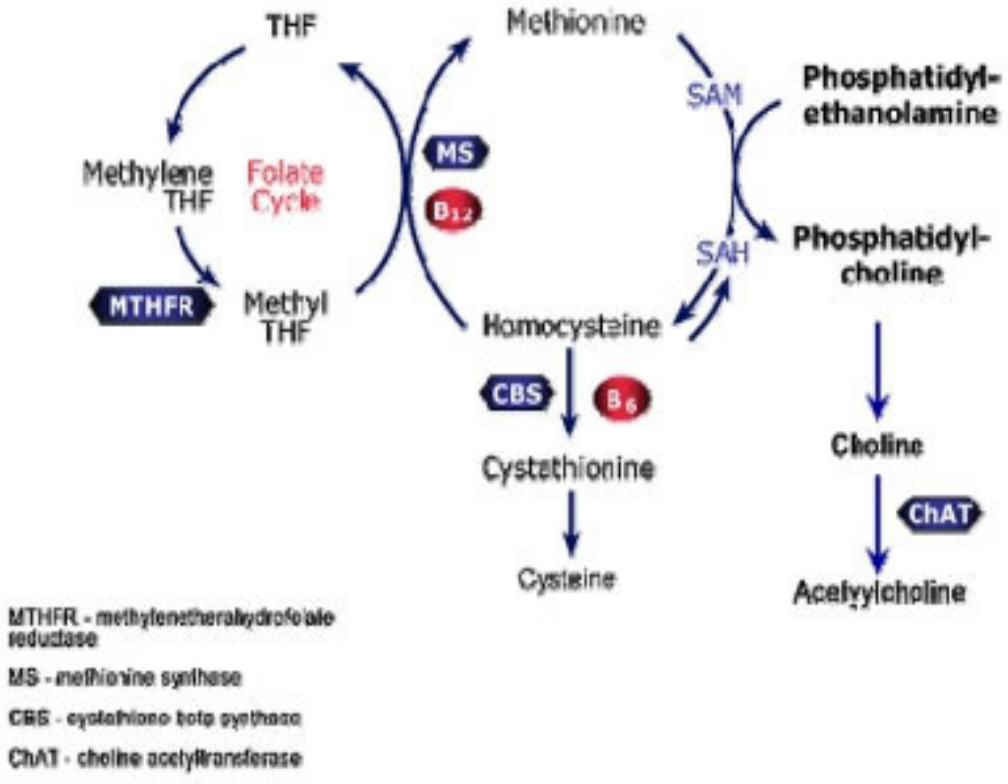
-Chronic renal insufficient

-Systemic lupus

-Neoplasm

-Hypothyroidism

HOMOCYSTIENE METABOLISM



HOMOCYSTEINE IN RELATION WITH ATHEROSCLEROSIS

HHCY

⇩

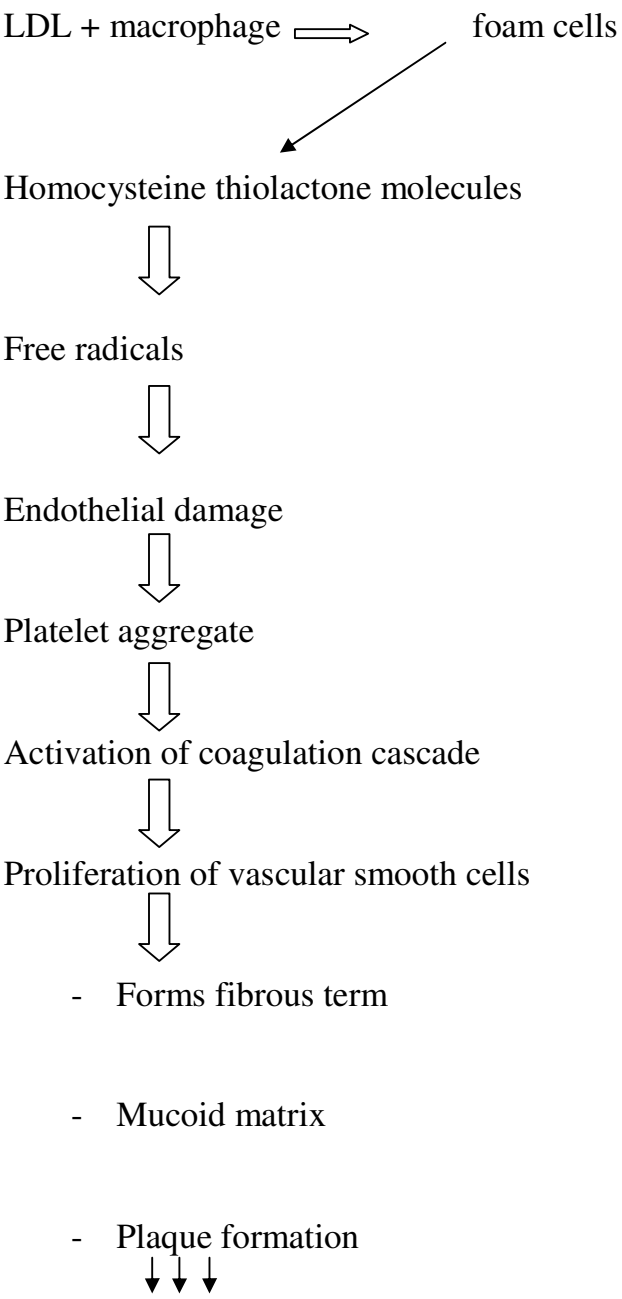
Increase production & reactive molecules

(Homocysteine thiolactone)

⇩

causes LDL aggregate

⇩


LDL + macrophage
foam cells
Homocysteine thiolactone molecules
Free radicals
Endothelial damage
Platelet aggregate
Activation of coagulation cascade
Proliferation of vascular smooth cells
- Forms fibrous term
- Mucoid matrix
- Plaque formation
Atherosclerosis

PHYSIOLOGICAL CHANGES IN PREGNANCY DUE TO HOMOCYSTEINE

Homocysteine concentration decreased in pregnancy due to

- Hemodilution
- Raised glomerular filtration rate
- Hormonal changes of pregnancy
- Increased fetal uptake

RELATION BETWEEN HOMOCYSTEINE AND VITAMIN B12/ FOLIC ACID DEFICIENCY

In vitamin b12 deficiency,

- Methyl malonic acid ↘ both are increased
  Homocysteine ↗

[OR]

- Methyl malonic acid level- elevated
  homocysteine level - normal

In folic acid deficiency,

- Methyl malonic acid level - normal
  homocysteine level is elevated

HOMOCYSTEINE EFFECTS ON PLACENTA

Placental development requires invasion into deciduas and its vasculature requires precise control of haemostasis and fibrinolysis.

Hormonal & related physiological changes affects

- clotting cascade

-fibrinolytic cascade

-platelet physiology

Placenta mediated diseases

- Infarction
- Abruption
- Pre eclampsia
- Recurrent pregnancy loss

- Increased Homocysteine
- Folate deficiency
- Homozygous state for MTHFR C677T

Homozygozity for MTHFR thermolabale variant isolated from placental tissue (daly et al, 1988]-21

Maternal folate homocysteine MTHFR defect not only associated with serum but also from placenta itself

EVALUATION AND FOLLOW UP

History

- Pattern, trimester, and characteristics of prior pregnancy losses
- History of subfertility or infertility
- Menstrual history
- Prior or current gynecologic or obstetric infections
- Signs or symptoms of thyroid, prolactin, glucose tolerance and hyperandrogenic disorders (including polycystic ovarian syndrome)
- Personal or familial thrombotic history
- Features associated with the antiphospholoid syndrome (thrombosis, false positive test for syphilis)
- Other autoimmune disorders
- Medications
- Environmental exposures, illicit and common drug use 9particularly caffeine, alcohol, cigarettes, and in utero diethylstilbestrol exposure)
- Genetic relationship between reproductive partners
- Family history of recurrent spontaneous abortion, of obstetric complications, or of any syndrome associated with embryonic or fetal losses

- Pervious diagnostic test and treatments, including, if available, chromosome testing on products of conception physical examination

a. General ophysical examination with particular attention to:

a. Obesity

b. Hirsutism/acanthosis

c. Thyroid examination

d. Breast examination/galactorrhea

e. Pelvic examination

1. Anatomy

2. Infection

3. Trauma

4. Estrogenization

5. Masculinization

LABORATORY

1. Parental peripheral blood karyotype

2. Chromosome testing on products of conception

3. Hysterosalpingography, three-dimensional transvaginal sonography, sonohysterography, or office hysteroscopy, followed by hestroscopy/laproscopy, if indicated

4. Thyroid stimulating hormone leve, serum prolatin level if indicated

5. Anticardiolipin antibody levels (lgG and lgM)

6. Lupus anticoagulant (activated partial thromboplastin time or Russell viper venom)

7. Anti-β2-glycoprotein-1 antibodies (lgG and lgM)

8. Complete blood count with platelets

9. Factor V leiden, G20210A prothrombin gene mutation, protein S activity, homocysteine level, activated protein c resistance (in white patients with suspicious family history)[9]

10.Protein C activity, antithrombin level if personal or family history of venous thromboembolic events

MANAGEMENT

ANTITHROMBOTIC THERAPY

Antithrombotic medications- combined use of low dose asprin (75 to 80mg/day) and subcutaneous unfractioned heparin (5000 to 10000 units twice daily) during pregnancy appears to be efficacious

Also low molecular weight heparin with low dose asprin in recurrent pregnancy loss with APS appears to be efficacious

If a venous thromboembolic event occurs during the index pregnancy post hospitalization management requires therapeutic anti coagulation:

- UFH :10000 to 15000 U s.c every 8 to 12hrs (monitor to keep aPTT 1.5 to 2.5 times normal)
- LMWH: enoxaparan 40 to 80 mg s.c twice a day or dalteparin 5000 to 10000 U s.c twice a day (monitor Xa levels in third trimester)

If there is personal history of thromboembolic events or strong family history, treat with therapeutic anti coagulation

Post partum anti coagulation should be continued for 6 to 12 weeks- this does not interfere with breast feeding.

IMMUNOSUPRESSIVE THERAPY:

IV Ig therapy: Based on a large number of studies , ther remains a inconclusive evidence to suggest that use of IVIg in the treatment of patients with unexplained pregnancy loss has any benefit.

PROGESTERONE THERAPY:

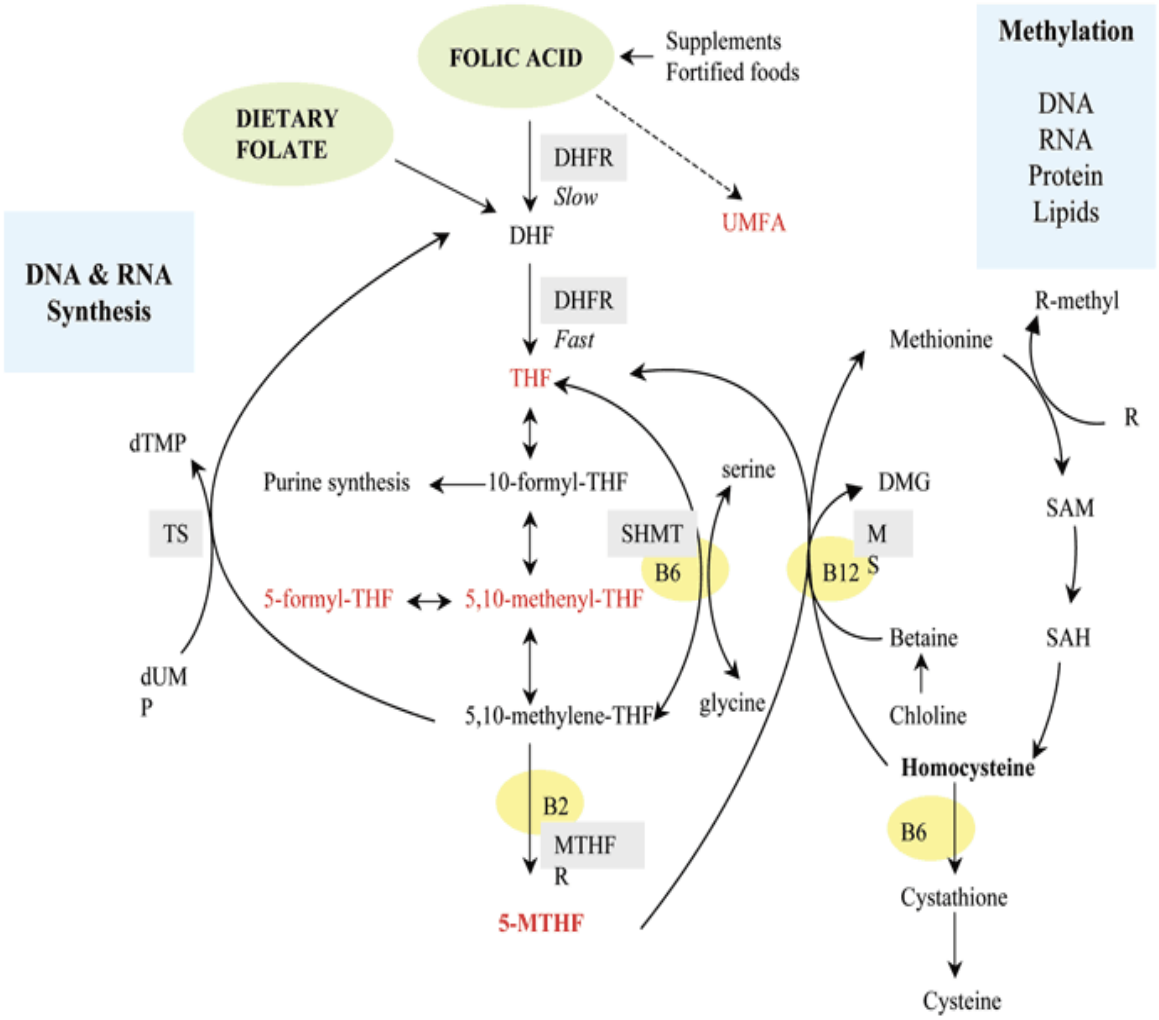
A number of studies demonstrates that progesterone either inhibits TH1 immunity or causes a shift from TH1 to TH2 type responses

Intra lipid infusion and TNFα inhibition therapy for treatment of recurrent pregnancy loss should only be administered under an institutional review board approved protocol.

PREDNISOLONE THERAPY :

Pregnancy outcomes for treated and control patients were similar . However the incidence of maternal diabetes and hypertension and the risk of premature delivery were all increased among those with treated with prednisolone and aspirin.

FOLIC ACID METABOLISM



CAUSES OF FOLIC ACID DEFICIENCY:

Decrease in folate adequacy

Impending folate deficiency

Overt folate deficiency

ADVERSE EFFECTS OF FOLIC ACID DEFICIENCY:

- Defective maturation of red blood cells.
- Megaloblastic anaemia.
- Cardiovascular diseases along with homocystienuria.
- Stroke.
- Infertility.
- Recurrent pregnancy losses due to neural tube defects.

NEURAL TUBE DEFECTS:

- Neural tube : The neural plate undergoes a change in shape to create and infolding and closure to form the neural tube.

- This structure develops into brain and spinal cord.

- Neural tube closure occurs between 22 and 28 days after conception

- Develops during first weeks of pregnancy (6 weeks after last menstrual period)

- Neural tube defects are a group of congenital birth defects that affect the central nervous system viz. spina bifida, anencephaly, encephalocele.

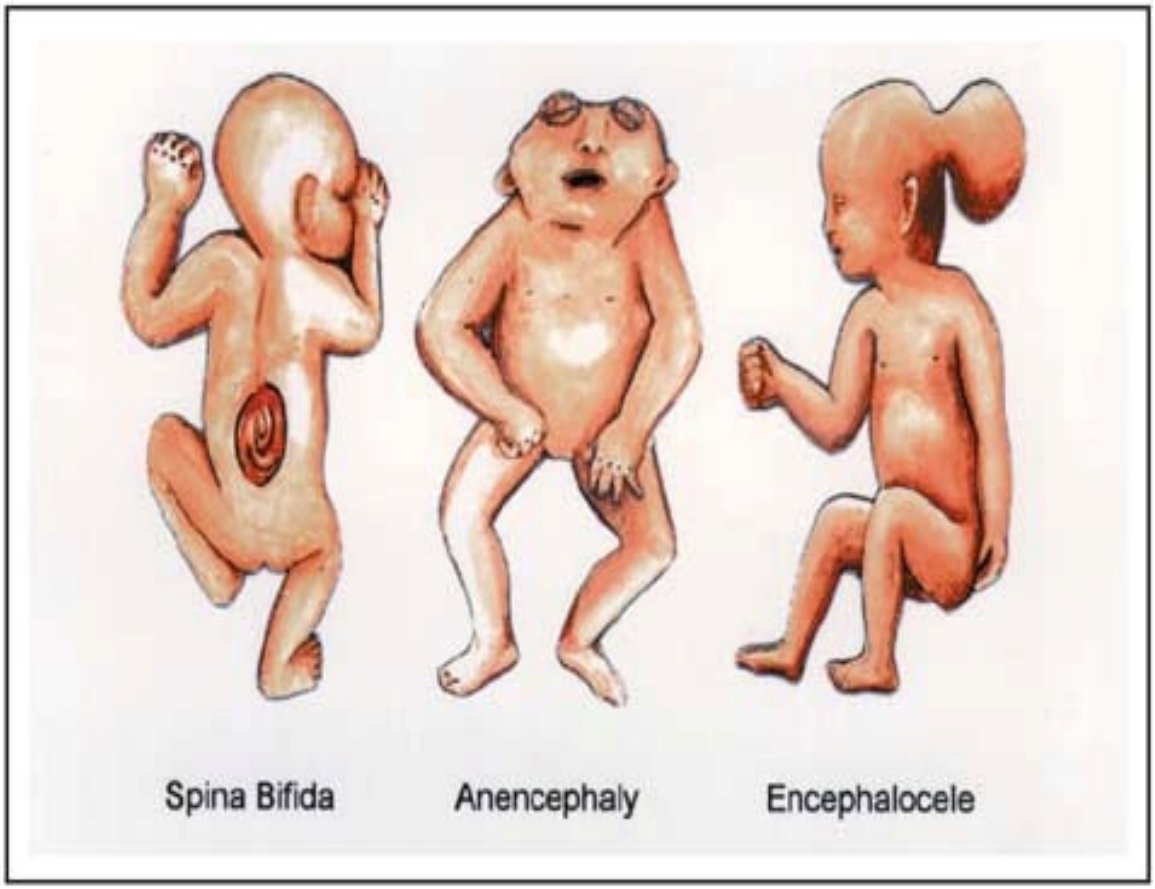
- Most common types are spina bifida and anencephaly

INCIDENCE

Spina bifida – 54 live births/yr

Anencephaly – 13live births/yr

Encephalocele – 13 live births/yr



SPINA BIFIDA

- Maldevelopment of neural tube in the lower part (spine)
- It is characterized by protrusion of spinal cord components outside the body
- Most common region- lumbar or lumbosacral

ANENCEPHALY:

- It results from improper development of the upper portion of the neural tube (brain)
- It is a fatal condition, characterized by severe mal formation of the brain accompanied by facial abnormalities and absence of the skull
- Many anencephaly affect pregnancies result in mis carriage and infants born with this condition die soon after birth (few hours to a few days)

ENCEPHALOCELE:

- It is a condition in which the brain protrude outside the skull in a sac of skin
- Children born with encephalocele usually live but suffer from mental disabilities.10% of neuraltube defects are due to encephalocoele

CAUSES OF NEURAL TUBE DEFECTS

- Spontaneous development (multi factorial-genes, environment)
- Chromosomal abnormalities (10 to 15%), genetic syndromes (3%)
- Nutritional folate deficiency (50%), inherited disorder of folate metabolism
- Maternal conditions, medications (teratogens- 1.5%)

MATERNAL RISK FACTORS

- Lower socio economic status
- Prior NTD- affected pregnancy
- Use of anti seizure treatment
- Poorly controlled insulin dependent diabetes
- Ethnicity

RISK OF RECURRENCE:

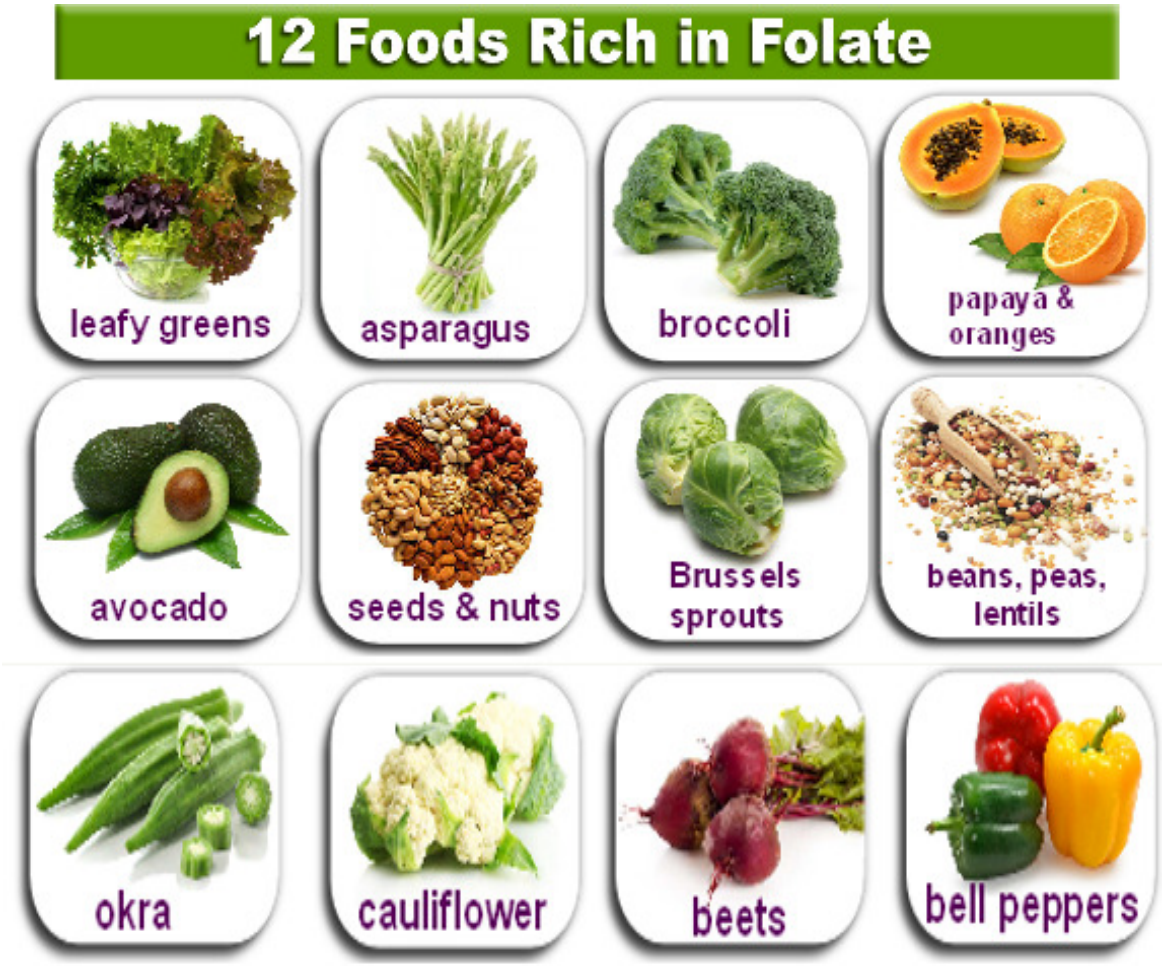
- For a mother who has NTD (1 in 25).
- For a couple with prior affected pregnancy (1 in 25)
- For a couple with two prior affected pregnancies (1 in 10)

FOLIC ACID DEFICIENCY DUE TO MEDICATIONS:

- Valproic acid
- Metformin
- Trimethoprim
- Methotrexate

PREVENTION OF NEURAL TUBE DEFECTS

- 50 to 70% of NTDs can be prevented by consumption of 400µ gms of synthetic folic acid per day
- Also consumption of folic acid from supplements or fortified foods
- Food rich in folate levels:
- Low in calories
- Low in fat
- Cholesterol free
- Rich in other vitamins and minerals viz. beta carotene, vit c, phytonutrients.



PATHOPHYSIOLOGY OF HOMOCYSTEINE METABOLISM:

Homocysteine metabolism altered in young patients with myocardial infarctionand MTHFR C667Thomozygosity [shwartz et al].

⇩

Homocysteine increased levels

⇩

endothelial dysfunction

vessel dilatation

Defective chorinic vascularisation is associated with embryonic death.

Diagnosed byhistopathology and image analysis system and cd34 Immunohistocnemistry[tevel de et al].

Parameters studied inthis placenta are

1. median vascular area
2. perimeter
3. number of vascular elements and measured chorionic area median area perimeter and diameter are measured per vascular elemaent in relation to maternal plasma homocysteine levels.

HOMOCYSTEINE AND PREGNANCY COMPLICATIONS

RECURRENT MISCARRIAGE

Wouters et al. were the first to report the association between HHCh and repeated miscarriage. 14% of women –primaryrepeated miscarriage while 33%of patients - secondary repeated miscarriage (after having had normal pregnancies) had HHCh. Studies says that damage to the decidual or chorionic vessels,and thus disrupts the implantation .Quere et al.[83] reported that, in a retrospective review of 100 patients presenting with a clinical picture of repeated miscarriage, 12% had HHCh, 20% were homozygotes for the thermolabile mutation of MTHFR, and 15% had low levels of folic acid.

HOMOCYSTEINE AND PREECLAMPSIA

Vascular pathway along with vitamin B12 and folic acid also affects pregnancy outcome.

In this study – made in ahmedabad vitamin B12, homocysteine , folic acid levels are measured using fluorescence polarized immunoassay .

Maternal uteroplacental circulation and fetal umbilical placental circulation are affected and vascular damage occurs.

Study group comprises 40 antenatal women divided into two groups.

GROUP 1: 28 to 40 weeks of gestation.

GROUP 2: 36to 40 weeks of gestation.

Each group divided into two divisions.

FIRST DIVISION: 20 women with normotensive.

SECOND DIVISION: 20 women with BP > 140/90 along with proteinuria.

Results:

P value < 0. 05 between control and study group , which is more significant.

P value < 0.001between study group 1 and 2 , which is also significant.

INFERENCE: Homocysteine- 5- 15 µmol/ L as normal value.

Study group 1- 13.45 +/- 4.40

Study group 2- 19.96 +/- 6.43

-all these findings are supported by walker et al. [2]

Increased homocysteine levels are seen in patients with pre-eclampsia where conversion of spiral arteries from highly tortuous thickened walls to flaccid sinusoidal contents of low resistance occurs. So muscular coats of spiral arteries are retained and more susceptible to hprmonal , maternal and neuronal constrictor influences(singh urmila et al).[1]

Power et al[3]– analysis shows that increased homocysteine levels in eclamptic patients.

Hogg et al[4] – also says that increased homocysteine levels in pregnancy induced hypertension and pre-eclampsia.

HOMOCYSTEINE LEVELS AND P VALUES:

Homocysteine levels correlate with severity of pre-eclampsia and Pvalue <0.017 which is more significant(Gupta et al).[1]

Lvoz et al – studied homocysteine levels in normal and pre-eclamptic patients and showed that homocysteine levels are increased in pre-eclamptic patients with P value 0.05.

Cottal M.Mulley et al and Truding BJ et al – also support the same findings.[12,115]

Area et al – folic acid , B 12, homocysteine are studied in pre-eclamptic patients which shows that increased homocysteine levels in pre- eclamptic women suggest endothelial damage.

HOMOCYSTEINE AND IUGR:

Most common cause for fetal growth restriction is maternal hypertension and especially pre-eclampsia. Growth restriction may be isolated or in association with pre-eclampsia. This affects 5 to 10% of all pregnancies.

Increased homocysteine levels in severe pre-eclampsia causes IUGR which suggests highly significant poisitive correlation between homocysteine and asymmetric di-methyl arginine(ADMA)

- all these are supported Lind Bled et al and Mao et al.[115,116]

FACTORS ASSOCIATED WITH EARLY PREGNANCY LOSS:

- Factor leiden mutation
- Activated protein c resistance
- Prothrombin G20210A mutation
- Protein s mutation
- MTHFR mutation, protein c and anti-thrombin deficiencies.[9]

HOMOCYSTEINE AND ABRUPTION PLACENTA

Hyperhomacysteinemia induce endothelial cell injury and disfunction leads to thrombiembolism and defects within placenta vascular bed(devries et al 1997)[19]

Smoking also increases homocysteine levels in placenta

Nicotine

Vasoconstrictor effect on utrine artery and amblical artery

Hence carboxyhemoglobin interferes with oxygenation

Nicotin and carbon monoxide croses placenta and levels increases in fetal circulation 15% higher than blood levels (luck et al 1985,andres et al2000)

Concentration of nicotine in amniotic fluid is 88% higher than in maternal plasma (luck et al 1985)

Homocysteine ,aproduct in the metabolism of essential amino acid methionine (steeger theunissen et al 2004)[94]and this metabolism involves 5,10 mthfr, folate,vitamin b6 , vit B12 (ray and laskin 1999, eskes 2001)[23,24,73,114]

Increased homocysteine levels causes endothelial cell injury and endothelial dysfunction leadin on to thromboembolism (de vries et al)[19]

There is an association factor between hyper homocystemia and placental abruption (goddgin wessel et al 1997, ray and laskin 1999, vollet et al 2000, steegers theunissen 2004)[94,114,113]

Folate deficiency is also a risk factor for placental abruption. Those who do not use folic and multi vitamin tablets had 26% increased risk for placental abruption (nilsen et al 2008). 15 to 20% of placental abruption attributable to smoking (arananth et al 1999). Inherited and acquired thrombophilias increase risk of venous thrombo embolism and adverse pregnancy outcome.

Kupfer mine et al 1999 says that patients with preeclampsia IUGR still births, placental abruption had heritable or acquired thrombophilias

Thrombophilias associated with abruption include

- MTHFR defeciency
- Heterozygous factor 5 leiden mutation (kupfer mine et al 1999, faahinnet robertson et al)
- Prothrombin gene mutation
- Protein C & S deficiency
- Lupus anticoagulant
- Anti cardiolipin antibodies (oyelese, anaanth 2006)

- Homozygous MTHFR point mutation 677C to T transition associated with placental abruption (ray and laskin et al 1999, eakes 2001, muk et al 2004)[24,114]

In finnish study, M3857 polymorphism is seen in factor 5 gene mutation Hyperhomocystenimia along with thrombophilias incresces risk of placental abruption 3 - 7 fold (eskes 2001)24

FETAL DEATH

Burke et al did however observe a 12% miscarriage rate and 10% perinatal death rate in the frequency of fetal death after supplementation with folic acid and multivitamins in a general population.

NEURAL TUBE DEFECTS

The association between neural tube defects (NTDs) and HHCh.

NTDs are not due to a direct action of HC, but indirectly due to a functional abnormality of methionine synthetase.

Folic acid deficiency and congenital abnormalities of MTHFR can both be responsible for NTDs and for HHCh. [94]

WHO ARE ALL THE PATIENTS TO BE TESTED FOR HOMOCYSTEINE LEVELS??

- Unexplained blood clots
- Unexplained atherosclerosis
- Coronary heart disease
- Heart attack
- Stroke.

WHO ARE ALL THE PATIENTS TO BE SCREENED FOR MTHFR MUTATION??

Previous history of women with birth of spina bifida and anencephaly child- can be screened.Ther is no specific indication to perform MTHFR genetic testing. Immaterial of mutation , dietary intervention per se and supplementation with vitamin B12 , B6 and folic acid is sufficient.

HOW CAN YOU LOWER HOMOCYSTEINE LEVELS??

- Good source folate in fruits and vegetables,
- fortified breads,
- Lentis
- Chick peas
- Asparagus

- Spinach and
- Most beans – all these supplements will break down homocysteine levels in blood and thus homocysteine levels decreases.
- 0.4mg of folic acid tablet decreases neural tube defects.
- 4 mg of folic acid tablets recommended for elevated homocysteine levels.[Erickson et al 72]

STUDY DETAIL

This study was conducted over a period of 12 months at department of Obstetrics and Gynaecology, Govt.R.S.R.M. Lying in Hospital attached to STANLEY MEDICAL COLLEGE, Royapuram, Chennai.

STUDY PERIOD

The period of study was from JANUARY 2015 – DECEMBER 2015

STUDY DESIGN

Observational study

METHODOLOGY

- Study population includes patients with pregnancy loss within 13 weeks of menstrual age
- To measure fasting homo cysteine & folic acid levels

INCLUSION CRITERIA

CASES –

- Patients with pregnancy loss within 13 weeks of menstrual age

CONTROLS –

- Patients attending ante natal outpatient department who had at least one live child with no history of previous abortions.

JUSTIFICATION → INCREASED homocystine and DECREASED folic acid level in patients with pregnancy loss & treating patients with FOLIC ACID & Multi VIT tablets.

EXCLUSION CRITERIA

Patients with

- Increased serum creatinine
- Increased serum alanine amino transferase
- Ectopic pregnancy
- Molar pregnancy
- Chronic hyper tension
- Diabetes mellitus
- Preexisting liver or renal disorder
- History of thromboembolism
- Abruptio placenta
- Pre term labour
- Anemia
- Smoking
- B12 & folic acid supplementation

All pregnancies to be confirmed by a positive urinary hCG test or ultrasound imaging.

• Fasting Blood sample taken after obtaining consent from the Patient

• For those with elevated homocysteine B6 and B12 added along with folic acid tablets

• Pedigree analysis of the patients done detail

MATERIAL AND METHODS

Between JANUARY 2015 to DECEMBER 2015, 100 women who suffered early pregnancy losses, attending our genetic clinic and antenatal OP were evaluated clinically and 100 women were enrolled for this study. Pregnancy Loss within 13 weeks gestation is enrolled in my study with confirmation by biochemical pregnancy test [β-human chorionic gonadotrophin (HCG 100 IU/l] and/or sonography. Ectopic pregnancies or elective terminations of gestations were excluded. They were categorized as primary and secondary aborters, based on whether they had atleast one pregnancy beyond 16 weeks of gestational age. A control group of 100 women with normal menstrual history and an obstetric history of uncomplicated pregnancies along with atleast one live child. All pregnancies confirmed by a positive urinary hCG test or ultrasound imaging. Detailed history with pedigree analysis done. The patients and controls did not take any vitamin B supplementation or oral contraceptives 6 months before performing homocysteine test. Fasting EDTA Blood sample was taken after obtaining informed consent from the patient at 0800 hours.

Homocysteine levels were measured after overnight fasting.Women were excluded if they had elevated serum creatinine or SGOT.None of the

subjects of either the study or the control group had a known endocrine dysfunction or suffered from gastrointestinal, hepatobiliary, renal or vascular disease. Patients with neurological disorders such as epilepsy were also excluded. Before admittance,informed consent was obtained from all subjects.

In four women other investigations revealed abnormalities like thyroid dysfunction, gestational diabetes, bicornuate uterus etc. Total homocysteine concentration was measured by enzymatic photometric method, after centrifugation and storing. out of 100 Patients, 21 women were considered hyperhomocysteinemic and 41 women with decreased folic acid levels. These patients started on oral folicacid supplementation. For those with elevated homocysteine, vitamin B6 and B12 were added.

Results are given as Mean, Median, Standard Deviation (SD). 95% confidence interval was also calculated. Consequently statistical significance was determined using F-test, Pearson Chi square test, Fischer linear test. A p-value <0.001 was considered to be a highly significant value.

RESULTS AND ANALYSIS

Age in years * Group

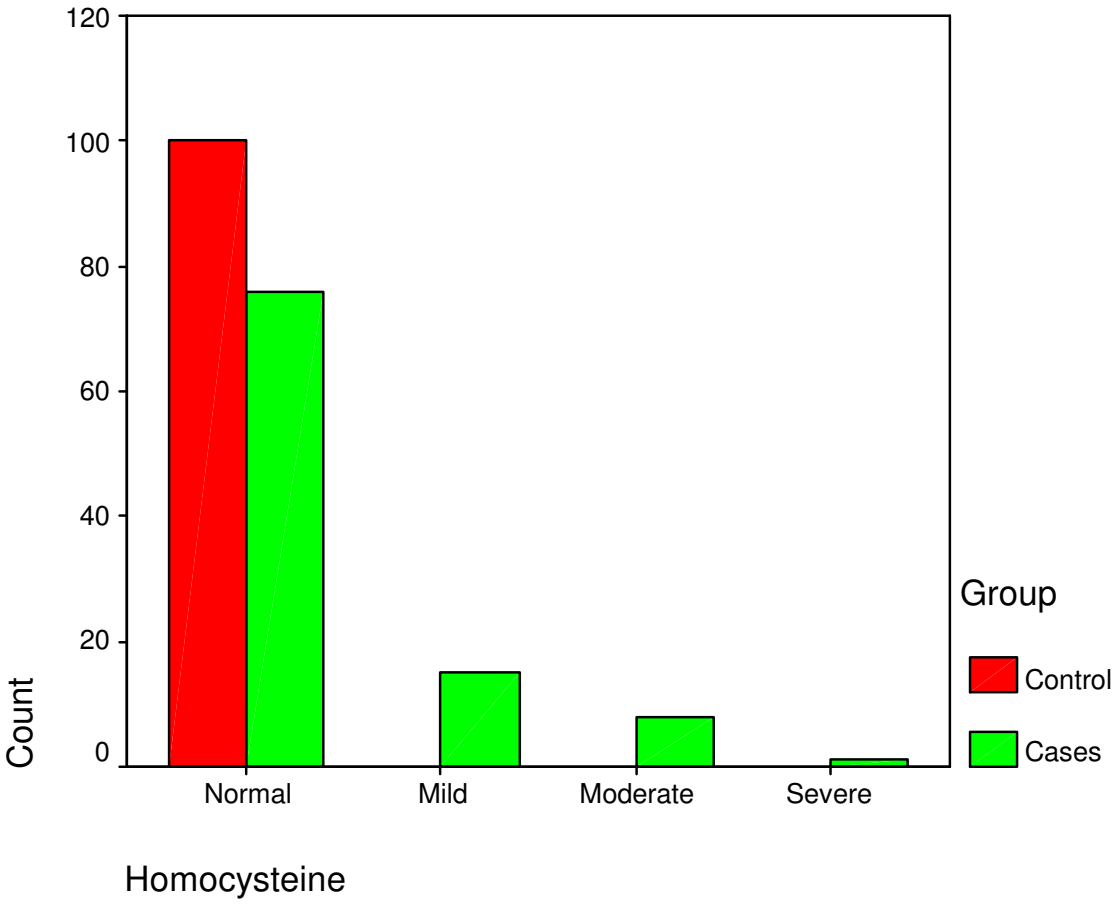
			Group		Total	P VALUE
			Control	Cases		
	18-20	Count	13	7	20	
AGE IN YEARS		% within Age in years	65.0%	35.0%	100.0%	
		% within Group	13.0%	7.0%	10.0%	
	21-25	Count	31	37	68	
		% within Age in years	45.6%	54.4%	100.0%	
		% within Group	31.0%	37.0%	34.0%	0.481
	26-30	Count	42	39	81	
		% within Age in years	51.9%	48.1%	100.0%	
		% within Group	42.0%	39.0%	40.5%	
	31-35	Count	13	14	27	
		% within Age in years	48.1%	51.9%	100.0%	
		% within Group	13.0%	14.0%	13.5%	
	36-40	Count	1	3	4	
		% within Age in years	25.0%	75.0%	100.0%	
		% within Group	1.0%	3.0%	2.0%	
Total		Count	100	100	200	
		% within Age in years	50.0%	50.0%	100.0%	
		% within Group	100.0%	100.0%	100.0%	

This table shows age in years comparison in which higher no of women falls in 25- 30 yrs and shows pvalue of 0.4 which is not much significant

Homocysteine * Group

			Group		Total	P VALUE
			Control	Cases		
Homocysteine	Normal	Count	100	76	176	** <0.001
		% within Homocysteine	56.8%	43.2%	100.0%	
		% within Group	100.0%	76.0%	88.0%	
	Mild	Count	0	15	15	
		% within Homocysteine	.0%	100.0%	100.0%	
		% within Group	.0%	15.0%	7.5%	
	Moderate	Count	0	8	8	
		% within Homocysteine	.0%	100.0%	100.0%	
		% within Group	.0%	8.0%	4.0%	
	Severe	Count	0	1	1	
		% within Homocysteine	.0%	100.0%	100.0%	
		% within Group	.0%	1.0%	.5%	
Total		Count	100	100	200	
		% within Homocysteine	50.0%	50.0%	100.0%	
		% within Group	100.0%	100.0%	100.0%	

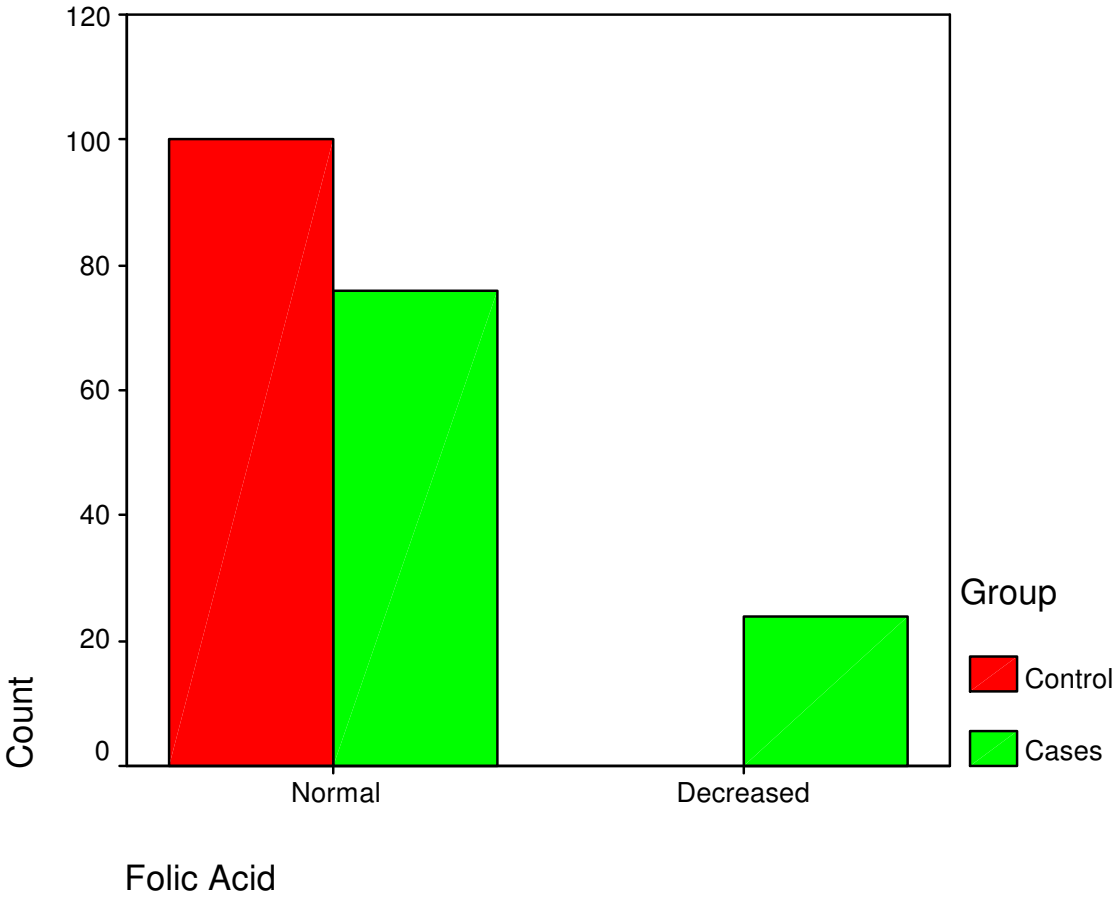
This table shows homocysteine group with cases and controls and pvalue is 0.001 which is more significant.


120
100
80
60
40
20
0
Count
Normal
Mild
Moderate
Severe
Homocysteine
Group
Control
Cases

Folic Acid * Group

			Group		Total	P VALUE
			Control	Cases		
Folic Acid	Normal	Count	100	76	176	
		% within Folic Acid	56.8%	43.2%	100.0%	
		% within Group	100.0%	76.0%	88.0%	
	Decreased	Count	0	24	24	
		% within Folic Acid	.0%	100.0%	100.0%	0.001
		% within Group	.0%	24.0%	12.0%	
Total		Count	100	100	200	
		% within Folic Acid	50.0%	50.0%	100.0%	
		% within Group	100.0%	100.0%	100.0%	

This tabular column shows folic acid group with cases and controls in which is more significant <0.001


120
100
80
60
40
20
0
Count
Normal
Decreased
Folic Acid
Group
Control
Cases

T-Test

Group Statistics

	Group	N	Mean	Std. Deviation	P VALUE
Age in years	Control	100	25.76	4.274	0.205
	Cases	100	26.54	4.400	

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Age in years	Equal variances assumed	.030	.864	-1.272	198	.205	-.78	.613	-1.990	.430
	Equal variances not assumed			-1.272	197.832	.205	-.78	.613	-1.990	.430

T-Test

Group Statistics

	Group	N	Mean	Std. Deviation	P VALUE
Homocysteine	Control	100	10.187	2.5718	
	Cases	100	13.847	12.0395	0.003

Homocysteine levels with mean and standard deviation are compared and p value is more significant 0.003

T-Test

Group Statistics

	Group	N	Mean	Std. Deviation	P VALUE
Folic Acid	Control	100	13.916	3.7312	0.001
	Cases	100	11.847	5.1291	

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Folic Acid	Equal variances assumed	13.510	.000	3.262	198	.001	2.069	.6343	.8181	3.3197
	Equal variances not assumed			3.262	180.856	.001	2.069	.6343	.8174	3.3204

Oneway

Descriptives

Homocysteine

No of abortion	N	Mean	Std. Deviation	P VALUE
1	24	9.199	4.0682	
2	32	11.947	6.2198	<0.001
3	24	12.512	7.1332	
4	20	24.065	21.5635	
Total	100	13.847	12.0395	

This tabular column based on number of abortions in homocysteine group.

mean and standard deviation values are calculated and pvalue is 0.001.

ANOVA

Homocysteine

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2765.088	3	921.696	7.638	.001
Within Groups	11584.918	96	120.676		
Total	14350.006	99			

Sum of squares and mean squares are calculated and p value is more significant

Post Hoc Tests

Multiple Comparisons

Dependent Variable: Homocysteine

Tukey HSD

(I) Number of abortion	(J) Number of abortion	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1	2	-2.748	2.9664	.791	-10.504	5.008
	3	-3.313	3.1712	.724	-11.605	4.978
	4	-14.866(*)	3.3260	.000	-23.562	-6.170
2	1	2.748	2.9664	.791	-5.008	10.504
	3	-.566	2.9664	.998	-8.321	7.190
	4	-12.119(*)	3.1313	.001	-20.306	-3.932
3	1	3.313	3.1712	.724	-4.978	11.605
	2	.566	2.9664	.998	-7.190	8.321
	4	-11.553(*)	3.3260	.004	-20.249	-2.857
4	1	14.866(*)	3.3260	.000	6.170	23.562
	2	12.119(*)	3.1313	.001	3.932	20.306
	3	11.553(*)	3.3260	.004	2.857	20.249

.

Homogeneous Subsets

Homocysteine

Tukey HSD

Number of abortion	N	Subset for alpha = .05	
		1	2
1	24	9.199	
2	32	11.947	
3	24	12.512	
4	20		24.065
Sig.		.720	1.000

Oneway

Descriptives

Folic Acid

	N	Mean	Std. Deviation	P VALUE
1	24	13.268	4.0356	0.004
2	32	12.511	5.3019	
3	24	12.564	5.0072	
4	20	8.221	4.8333	
Total	100	11.848	5.1291	

Folic acid group shows mean and standard deviation values in which pvalue are calculated 0.004which is more significant

ANOVA

Folic Acid

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	337.978	3	112.659	4.772	.004
Within Groups	2266.518	96	23.610		
Total	2604.496	99			

Post Hoc Tests

Multiple Comparisons

Dependent Variable: Folic Acid

Tukey HSD

(I) Number of abortion	(J) Number of abortion	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1	2	.757	1.3121	.939	-2.673	4.188
	3	.704	1.4027	.958	-2.963	4.372
	4	5.048(*)	1.4711	.005	1.201	8.894
2	1	-.757	1.3121	.939	-4.188	2.673
	3	-.053	1.3121	1.000	-3.483	3.378
	4	4.291(*)	1.3850	.013	.669	7.912
3	1	-.704	1.4027	.958	-4.372	2.963
	2	.053	1.3121	1.000	-3.378	3.483
	4	4.344(*)	1.4711	.020	.497	8.190
4	1	-5.048(*)	1.4711	.005	-8.894	-1.201
	2	-4.291(*)	1.3850	.013	-7.912	-.669
	3	-4.344(*)	1.4711	.020	-8.190	-.497

Homogeneous Subsets

Folic Acid

Tukey HSD

Number of abortion	N	Subset for alpha = .05	
		1	2
4	20	8.221	
2	32		12.511
3	24		12.564
1	24		13.268
Sig.		1.000	.948

Frequencies

Age in years

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	18-20	20	10.0	10.0	10.0
	21-25	68	34.0	34.0	44.0
	26-30	81	40.5	40.5	84.5
	31-35	27	13.5	13.5	98.0
	36-40	4	2.0	2.0	100.0
	Total	200	100.0	100.0	

Number of abortion

		Frequency	Percent
Valid	1	24	24.0
	2	32	32.0
	3	24	24.0
	4	20	20.0
	Total	100	100.0

Homocysteine

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Normal	176	88.0	88.0	88.0
	Mild	15	7.5	7.5	95.5
	Moderate	8	4.0	4.0	99.5
	Severe	1	.5	.5	100.0
	Total	200	100.0	100.0	

In homocysteine group cumulative percentage is calculated .mild levels shows 95%moderate levels shows 99.5%.severe levels shows 100 %

Folic Acid

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Normal	176	88.0	88.0	88.0
	Decreased	24	12.0	12.0	100.0
	Total	200	100.0	100.0	

Cumulative percentage for folic acid levels are calculated which shows

88%among normal patientsand decreased folic acid levels shows 100%

DISCUSSION

Multiple mechanisms play a role in the etiology of pregnancy loss , viz

-Immunological disorders

-Genetic disorders

-Endocrine disorders

-Psychological disorders

-Inherited disorders

- are responsible for embryo loss(Bulleti.,et al…1996).

- Moderate hyperhomocysteinemia also found to be risk factor for recurrent pregnancy loss(steegers Thunissen..et al -1992;Wouer et al…1993;Del Biaco et al…2004).[94]
- Hyperhomocysteinemia shows an increased risk in causing recurrent pregnancy loss – confirmed meta analysis report(Nelen et al…2000).[23,24]
- Lowering homocysteine concentration by vitamin B12 supplementation, shows a positive effect in several cases.
- After a few months of treatment, spontaneous pregnancies occurs in those patients who had previous pregnany loss (Quere et al..1998,2001;Candito et al…2003;Gueant et al…2004).[46,84,85,83]

- Daily supplementation with vitamin B12 and folic acid- redeuce homocysteine concentration (Homocysteine lowering collaboration- American Journal).
- Regarding MTHFR mutation , treatment is dietary intervention and supplementation with folic acid and vitamin B group.
- The amount depends upon the degree homocysteine elevation.
- Many unknowns remain regarding the impact of hyperhomocysteinemia pregnancy.
- Large scale of study and control groups needed to define relation between homocysteine , folic acid and pregnancy loss.

SUMMARY

- Our study comprises 100 recurrent pregnancy loss cases and 100 control cases.
- Out of 100 cases, 21 patients shows increased homocysteine levels and 24 patients shows decreased folic acid levels.
- Homocysteine group shows P value of 0.001, which is significant at 1% levels.
- Also folic acid group shows P value 0.001, which is also highly significant.
- In patients with increased homocysteine levels , vitamin B6 , vitamin B 12 along with folic acid tablets are given.
- This study shows there is no correlation of age with hyperhomocysteinemia and decresed folic acid levels.

CONCLUSION

Recent studies on early pregnancy loss and hyperhomocysteinemia suggested a positive association between the two.In the present study elevated fasting homocysteine concentrations along with decreased folic acid levels were associated with early pregnancy losses. The level showed no significant difference in ages.In my study Homocysteine group and folic acid group show a significant p value of less than 0.001. In animal studies folic acid supplementation seemed to improve survival of fetuses during early gestations and increases the number of living fetuses.In our study also folic acid supplementation along with B12 and B6 has an effect on lowering the homocysteinebut the still more studies are needed to conclude the effect of folic acid B6,B12 on pregnancy outcome.Still more intervention trials as well as prospective studies measuring folate and tHcy status before and during pregnancy are needed to establish the role of folic acid B6 and B12 either as predictors or etiologic factors for recurrent pregnancy losses.

We therefore believe that women with hyperhomocysteinemia should be identified earlier. The folic acid-vitamin B6,B12 combination, a nonteratogenic treatment, should be tried. As suggested by our case report, therapeutic normalization of hyperhomocysteinemia might lead to metabolic restoration, which may favor a successful pregnancy outcome.

BIBLIOGRAPHY

1. Singh U, Gupta HP, Singh RK, Shukla M, Singh R, Mehrotra SS, et al. A study of changes in homocysteine leels during normal pregnancy and pre-eclampsia. J Indian Med Assoc 2008; 106: 503-5.

2. Walker MC, Smith GN, Perkins SL, et al. Changes in homocysteine levels during normal pregnancy. Am J Obstet Gynecol 1999;180:660-4.

3. Powers RW, Evans RW, Majors AK et al. Plasma homocysteine concentration is increased in preeclampsia and associated with evidence of endothelial activation. Am J Obstet Gynecol 1998;179:1605-11

4. Hogg BB, Tamura T, Kelley E, et al. Second-trimester plasma homocysteine levels and pregnancy-induced hypertension, preeclampsia, and intrauterine growth restriction. Am J Obstet Gynecol 2000;183:805-9.

5. Ueland PM, Refsum H, Stabler SP et al. Total homocysteine in plasma or serum: methods and clinical applications. Clin Chem 1993;39:1764-79.

6. Refsum H, Ueland PM, Svardal AM. Fully automated fluorescence assay for determining total homocysteine in plasma. Clin Chem 1989;35:1921–7.

7. Andersson A, Hultberg B, Brattstrom L, Isaksson A. Decreased serum homocysteine in pregnancy. Eur J Chem Clin Biochem 1992;30:377–9.

8. Lentz SR. Mechanisms of thrombosis in hyperhomocysteinemia. Curr Opin Hematol 1998;5:343–9.

9. Grandone E, Margaglione M, Colaizzo D, et al. Factor V Leiden, C>T MTHFR polymorphism and genetic susceptibility to preeclampsia. Thromb Haemost 1997;77:1052–4.

10. Kanani PM, Sinkey CA, Browning RL, Allaman M, Knapp HR, Haynes WG. Role of oxidant stress in endothelial dysfunciton produced by experimental hyperhomocysteinaemia in humans. Circulation 1999; 100: 1161-8.

11. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998; 338:1042- 50.

12. Wang J, Trudinger BJ, Duarte N, Wilcken DE, Wang XL. Elevated circulating homocystine levels in placental vascular disease and associated pre-eclampsia. BJOG 2000; 107: 935-8

13. Mignini LE, Latthe PM, Villar J, Kilby MD, Carrolli G, Khan KS. Mapping the theories of Pre-eclampsia: the role of homocysteine. Obstet Gynecol 2005; 105: 411-25.

14. Noris M, Todeschini M, Cassis P, Pasta F cappellini A, Bonazzola S, Macconi D, Maucci R, Porrti F, Benigni A, Piccciolo C, Remuzzi G. L-arginine depletion in preeclampsia orient nitric oxide synthase toward oxidant species. Hypertention. 2004; 43: 614-22.

15. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlim MK. Preeclampsia: an endothelial cell disorders. American Journal of Obstetrics and Gynecology. 1989; 161: 1200-1204.

16. Walsh SW. Maternal-placental interactions of oxidative stress and antioxidants in preeclampsia, Semin Reprodective Endocrinology. 1998;16:93-104.

17. Benyo DF, Miles TM, Condrad KP. Hypoxia stimulates cytokines production by villous explants from human placenta. Journal of Clinical Endocrinology and Metabolism. 1997; 82: 1582-1588.

18. Many A, Hubel CA, Roberts MJ. Hyperurricemia and xanthine oxidase in preeclampsia revisited. American journal of Obstetrics and Gynecology. 1996; 174: 288-291

19. Coumans ABC, Huijgens PC, Jakobs C, Schats R, De Vries JIP, van Pampus MG, et al. Haemostatic and metabolic abnormalities in women with unexplained recurrent abortion.

HumReprod1999;

21.Graham IM, Daly LE, Refsum HM, Robinson K, Brattstro¨m LE, Ueland PM, et al. Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project. JAMA1997;277:

22.Boushey CJ, Beresford SAA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: Probable benefits of increasing folic acid intakes. J Am Med Assoc 1995;

23.Nelen WLDM, Steegers EAP, Eskes TKAB, Blom HJ. Genetic risk factor for unexplained recurrent early pregnancy loss. Lancet 1997;

24.Nelen WLDM, Van der Molen EF, Blom HJ, Heil SG, Steegers EAP, Eskes TKAB. Recurrent early pregnancy loss and genetic related disturbances in folate and homocysteine metabolism. Br J Hosp Med 1997 Jacques, P.F., Bostom, A.G., Williams, R.R., Ellison, R.C., Eckfeldt, J.H., Rosenberg, I.H., Selhub, J. and Rozen, R. (1996) Relation between folate status, a common mutation in methylenetetrahydrofolate reductase, and plasma homocysteine concentrations.Circulation, 93, 7–9.

25.Mills, J.L., McPartlin, J.M., Kirke, P.N., Lee, Y.J., Conley, M.R., Weir, D.G. and Scott, J.M. (1995) Homocysteine metabolism in pregnancies complicated by neural-tube defects. Lancet, 345, 149–151.

26.Nelen, W.L., Blom, H.J., Steegers, E.A., den Heijer, M. and Eskes, T.K. (2000) Hyperhomocysteinemia and recurrent early pregnancy loss: a meta-analysis. Fertil. Steril., 74, 1196–1199.

27.Agarwal A, Gupta S, Sharma RK. Role of oxidative stress in female reproduction. Reprod Biol Endocrinol 2005;3:28–47.

28.Agarwal A, Prabakaran S, Allamaneni S. What an andrologist / urologist should know about free radicals and why. Urology 2006;67:2–8.

29.Aubry F, Habasque C, Satie AP, et al. Expression and

regulation of the CC-chemokine monocyte chemoattractant protein-1 in rat testicular cells in primary culture. Biol Reprod 2000;62:1427–35.

30. Austin RC, Lentz SR, Werstuck GH. Role of hyperhomocysteinemia in endothelial dysfunction and atherothrombotic disease. Cell Death Differ 2004;11(Suppl 1):S56–64.

31. Azem F, Many A, Ben Ami I, et al. Increased rates of thrombophilia in women with repeated IVF failures. Hum Reprod 2004;19:368–70.

32. Azziz R. PCOS: a diagnostic challenge. Reprod Biomed Online 2004;8:644–8.
Bayraktar F, Dereli D, Ozgen AG, et al. Plasma homocysteine levels in polycystic ovary syndrome and congenital adrenal hyperplasia. Endocr J 2004;51:601–8.

33. Benchaib M, Braun V, Ressnikof D, et al. Influence of global sperm DNA methylation on IVF results. Hum Reprod 2005;20:768–73.

34. Bentivoglio G, Melica F, Cristoforoni P. Folinic acid in the treatment of human male infertility. Fertil Steril 1993;60:698–701.

35. Berger PB, Herrmann RR, Dumesic DA. The effect of estrogen replacement therapy on total plasma homocysteine in healthy postmenopausal women. Mayo Clin Proc 2000:75:18-23.

36. Berry RJ, Kihlberg R, Devine O. Impact of misclassification of in vitro fertilisation in studies of folic acid and twinning: modelling using population based Swedish vital records. BMJ 2005;330:815–7.

37. Bettahar-Lebugle K, Feugeas O, Wittemer C, Evolution of homocysteine during ovarian stimulation for IVF or ICSI. Gynecol Obstet Fertil 2000;30:121–8.

38. Bezold G, Lange M, Peter RU. Homozygous methylenetetrahydrofolate reductase C677T mutation and male

infertility. New Engl J Med 2001; 344:1172–3.

39. Birn H, Zhai X, Holm J, et al. Megalin binds and mediates cellular internalization of folate binding protein. FEBS J 2005;272:4423–30.

40. Blaise S, Alberto JM, Nedelec E, et al. Mild neonatal hypoxia exacerbates the effects of vitamin-deficient diet on homocysteine metabolism in rats. Pediatr Res 2005;57:777–82.

41. Blount BC, Mack MM, Wehr CM, et al. Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage: implications for cancer and neuronal damage. Proc Natl Acad Sci USA 1997;94:3290–5.

42. Boers GH, Smals AG, Trijbels FJ, et al. Unique efficiency of methionine metabolism in premenopausal women may protect against vascular disease in the reproductive years. J Clin Invest 1983;72:1971–6.

43. Botto LD, Yang Q. 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: a HuGE review. Am J Epidemiol 2000; 151:862–77.

44. Brattstrom L, Israelsson B, Olsson A, et al. Plasma homocysteine in women on oral oestrogen-containing contraceptives and in men with oestrogentreated prostatic carcinoma. Scand J Clin Lab Invest 1992;52:283–7.

45. Calhaz-Jorge C, Costa AP, Santos MC, et al. Peritoneal fluid concentrations of interleukin-8 in patients with endometriosis depend on the severity of the disorder and are higher in the luteal phase. Hum Reprod 2003;18:593–7.

46. Candito M, Magnaldo S, Bayle J, et al. Clinical B12 deficiency in one case of recurrent spontaneous pregnancy loss. Clin Chem Lab Med 2003;41:1026–7.

47. Chadwick LH, McCandless SE, Silverman GL, et al. Betainehomocysteine methyltransferase-2: cDNA cloning, gene sequence, physical mapping, and expression of the human and

mouse genes. Genomics 2000;70:66–73.

48.Chen Q, Ng V, Mei J, et al. Comparison of seminal vitamin B12, folate, reactive oxygen species and various sperm parameters between fertile and infertile males. Wei Sheng Yan Jiu 2001a;30:80–82.

49.Chen Z, Karaplis AC, Ackerman SL, et al. Mice deficient in Methylenetetra hydrofolate reductase exhibit hyperhomocysteinemia and decreased methylation capacity, with neuropathology and aortic lipid deposition. Hum Mol Genet 2001b;10:433–43.

50.Christensen B, Arbour L, Tran P, et al. Genetic polymorphisms in methylenetetrahydrofolate reductase and methionine synthase, folate levels in red blood cells, and risk of neural tube defects. Am J Med Genet 1999;84:151–7.

60.Cosentino MJ, Pakyz RE, Fried J. Pyrimethamine: an approach to the development of a male contraceptive. Proc Natl Acad Sci USA 1990;87:1431–5.

61.Coumans AB, Huijgens PC, Jakobs C, et al. Haemostatic and metabolic abnormalities in women with unexplained recurrent abortion. Hm Reprod 1999;14:211–4.

62.Czeizel AE, Vargha P. Periconceptional folic acid/multivitamin supplementation and twin pregnancy. Am J Obstet Gynecol 2004;191:790–4.

63.Czeizel AE, Metneki J, Dudas I. The higher rate of multiple births after periconceptional multivitamin supplementation: an analysis of causes. Acta Genet Med Gemellol (Roma) 1994;43:175–84.

64.Del Bianco A, Maruotti G, Fulgieri AM, et al. Recurrent spontaneous miscarriages and hyperhomocysteinemia. Minerva Ginecol 2004;56: 379–83.

65.Delgado-Reyes CV, Wallig MA, Garrow TA. Immuno histochemical detection of betaine-homocysteine Smethyltransferase in human, pig, and rat liver and kidney. Arch

Biochem Biophys 2001;393:184–6.

66. Di Simone N, Maggiano N, Caliandro D, et al. Homocysteine induces trophoblast cell death with apoptotic features. Biol Reprod 2003; 69:1129–34.

67. Folate metabolism and reproduction 235 Downloaded from http://humupd.oxfordjournals.org/ by guest on October 24, 2011 Dobson AT, Davis RM, Rosen MP, et al. Methylenetetrahydrofolate reductase C677T and A1298C variants do not affect ongoing pregnancy rates following IVF. Hum Reprod 2007;22:450–6.

68. Doerksen T, Benoit G, Trasler JM. Deoxyribonucleic acid hypomethylation of male germ cells by mitotic and meiotic exposure to 5-azacytidine is associated with altered testicular histology. Endocrinology 2000;141:3235–44.

69. Ebisch IM, van Heerde WL, Thomas CM, et al. C677T ethylenetetrahydrofolate reductase polymorphism interferes with the effects of folic acid and zinc sulfate on sperm concentration. Fertil Steril 2003;80:1190–4.

70. Ebisch IM, Peters WH, Thomas CM. Homocysteine, glutathione and related thiols affect fertility parameters in the (sub)fertile couple. Hum Reprod 2006a;21:1725–33.

71. Ebisch IM, Pierik FH, De Jong FH, et al. Does folic acid and zinc sulphate intervention affect endocrine parameters and sperm characteristics in men? Int J Androl 2006b;29:339–45.

72. Ericson A, Kallen B, Aberg A. Use of multivitamins and folic acid in early pregnancy and multiple births in Sweden. Twin Res 2001;4:63–66.

73. Eskes TK. Homocysteine and human reproduction. Clin Exp Obstet Gynecol 2000;27:157–67.

74. Farag NH, Barshop BA, Mills PJ. Effects of estrogen and psychological stress on plasma homocysteine levels. Fertil Steril 2003;79:256–60.

75.Favier M, Faure P, Roussel AM, et al. Zinc deficiency and dietary folate metabolism in pregnant rats. J Trace Elem Electrolytes Health Dis 1993;7:19–24.

76.Fenech M. The role of folic acid and Vitamin B12 in genomic stability of human cells. Mutat Res 2001;475:57–67.

77.Fowler B. The folate cycle and disease in humans. Kidney Int 2001;59(Suppl 78):S221–9.

78.Fowler B. Homocysteine: overview of biochemistry, molecular biology, and role in disease processes. Semin Vasc Med 2005;5:77–86.

79.Friso S, Choi SW, Girelli D, et al. A common mutation in the 5,10-methylenetetrahydrofolate reductase gene affects genomic DNA methylation through an interaction with folate status. Proc Natl Acad Sci USA 2002;99:5606–11.

80.Frosst P, Blom HJ, Milos R, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet 1995;10:111–3.

81.George L, Mills JL, Johansson AL, et al. Plasma folate levels and risk of spontaneous abortion. JAMA 2002;288:1867–73.

82.Gmyrek GB, Sozanski R, Jerzak M, et al. Evaluation of monocyte chemotactic protein-1 levels in peripheral blood of infertile women with endometriosis. Eur J Obstet Gynecol Reprod Biol 2005;122:199–205.

83.Gris JC, Perneger TV, Quere I, et al. Antiphospholipid /antiprotein antibodies, hemostasis-related autoantibodies, and plasma homocysteine as risk factors for a first early pregnancy loss: a matched case-control study. Blood 2003;102:3504–13.

84.Gueant JL, Candito M, Andres E, et al. Familial pernicious anaemia with hyperhomocysteinaemia in recurrent early pregnancy loss. Thromb Haemost 2004;92:1147–49.

85.Gueant JL, Gueant-Rodriguez RM, Anello G, et al. Genetic determinants of folate and vitamin B12 metabolism: a common

pathway in neural tube defect and Down syndrome? Clin Chem Lab Med 2003;41:1473–7.

86. Gueant-Rodriguez RM, Gueant JL, Debard R, et al. Prevalence of methylenetetrahydrofolate reductase 677T and 1298C alleles and folate status: a comparative study in Mexican, West African, and European populations. Am J Clin Nutr 2006;83:701–7.

87. Haggarty P, McCallum H, McBain H. Effect of B vitamins and genetics on success of in-vitro fertilisation: prospective cohort study. Lancet 2006;367:1513–19.

88. Hague WM. Homocysteine and pregnancy. Best Pract Res Clin Obstet Gynaecol 2003;17:459–69.

89. Hak AE, Polderman KH, Westendorp IC, et al. Increased plasma homocysteine after menopause. Atherosclerosis 2000;149:163–8.

90. Hall JG. Twinning. Lancet 2003;362:735–43.

91. Harmon DL, Woodside JV, Yarnell JW, et al. The common 'thermolabile' variant of methylene tetrahydrofolate reductase is a major determinant of mild hyperhomocysteinaemia. QJM 1996;89:571–7.

92. Hasbargen U, Lohse P, Thaler CJ. The number of dichorionic twin pregnancies is reduced by the common MTHFR 677C–.T mutation. Hum Reprod 2000;15:2659–62.

93. Henning BF61, Tepel M, Riezler R, et al.Vitamin supplementation during weight reduction – favourable effect on homocysteine metabolism. Res Exp Med (Berl) 1998;198:37–42.

94. Steegers-Theunissen, R.P., Boers, G.H., Trijbels, F.J. and Eskes, T.K. (1991) Neural-tube defects and derangement of homocysteine metabolism. N. Engl. J. Med., 324,199–200 Strobino B, Fox HE, Kline J, Stein Z, Susser M, Warburton D. Characteristics of women with recurrent spontaneous abortions and women with favorable reproductive histories. Am J Public Health. 1986 Aug. 76(8):986-91.

95. Summers PR. Microbiology relevant to recurrent miscarriage. Clin Obstet Gynecol. 1994 Sep. 37(3):722-9. Tulandi T, al-Took S. Endoscopic myomectomy. Laparoscopy and hysteroscopy. *Obstet Gynecol Clin North Am*. 1999 Mar. 26(1):135-48, viii.

96. Warburton D, Fraser FS. Spontaneous abortion risks in man: data from reproductive histories collected in a medical genetics unit. *Am J Hum Genet*. 1964 Mar. 16:1-25.

97. Watt JL, Templeton AA, Messinis I, Bell L, Cunningham P, Duncan RO. Trisomy 1 in an eight cell human pre-embryo. *J Med Genet*. 1987 Jan. 24(1):60-4.

98. Werler MM. Teratogen update: smoking and reproductive outcomes. *Teratology*. 1997 Jun. 55(6):382-8.

99. Whitely RJ. Herpes simplex virus. Fields BN, Knipe DM, eds. *Virology*. 2nd ed. New York, NY: Raven; 1990. 1874.

100. Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum*. 1999 Jul. 42(7):130911.

101. Strobino B, Fox HE, Kline J, Stein Z, Susser M, Warburton D. Characteristics of women with recurrent spontaneous abortions and women with favorable reproductive histories. *Am J Public Health*. 1986 Aug. 76(8):986-91. TURNITIN.COM

102. R. M. C. Dawson: *Data for Biochemical Research*, Oxford University Press, Oxford, 1989, 3rd Edition, p. 134, ISBN 0-19-855299-8.

103. Darby, William J.; Jones, Edgar (1 November 1945). "Treatment of Sprue with Synthetic L. casei Factor (Folic Acid, Vitamin M).". *Experimental Biology and Medicine* **60** (2): 259–262. doi:10.3181/00379727-60-15154P. Retrieved 13 December 2014.

104. Ural, Serdar H. (November 2008). "Folic Acid and Pregnancy". Kid's Health.

105. Weil, Andrew. "Supplements & Herbs (Vitamin B9-- Folate)". *MD*. www.drweil.com. Retrieved 2 April 2014.

106."Folate". *Patient Care & Health Info – Drugs and Supplements*. Mayo Clinic. 1 November 2013. Retrieved 11 January 2014.

107.Weinstein SJ, Hartman TJ, Stolzenberg-Solomon R et al. (November 2003). "Null association between prostate cancer and serum folate, vitamin B(6), vitamin B(12), and homocysteine". *Cancer Epidemiol. Biomarkers Prev.* **12** (11 Pt 1): 1271–2. PMID 14652294.

108.National Health Service U.K., "Anaemia, vitamin B12 or folate deficiency – Causes" http://www.nhs.uk/Conditions/Anaemia-vitamin-B12-and-folate-deficiency/Pages/Causes.aspx

109.National Center on Birth Defects and Developmental Disabilities (2012). "Neural Tube Defects (Annual Report)" (PDF). US Centers for Disease Control and Prevention.

110.Botez MI (1976). "Folate deficiency and neurological disorders in adults". *Med. Hypotheses* **2** (4): 135–40. doi:10.1016/0306-9877(76)90068-2. PMID 958035.

111.Shaw GM, Schaffer D, Velie EM, Morland K, Harris JA (May 1995). "Periconceptional vitamin use, dietary folate, and the occurrence of neural tube defects". *Epidemiology* **6** (3): 219–26. doi:10.1097/00001648-199505000-00005. PMID 7619926.

112.Mulinare J, Cordero JF, Erickson JD, Berry RJ (December 1988). "Periconceptional use of multivitamins and the occurrence of neural tube defects". *JAMA* **260** (21): 3141–5. doi:10.1001/jama.1988.03410210053035"Folic Acid". The PubChem Project.

113.Goddijin Wessel, T.A., wouters, M.G.A.J., Van der Molen, E.F.et al, (1996) hyperhomocystemia a risk factor for placental abruption or infarction

114.Ray JG, Laskin CA. Folic acid and homocyst(e)ine metabolic defects and the risk of placental abruption, pre-eclampsia and spontaneous pregnancy loss: a systematic review. Placenta 1999;20:519 –29.

115.Nelen WLDM, Blom HJ. Pregancy complications. In: Ueland PM, Rozen R, eds. MTHFR polymorphisms and disease. Georgetown, TX: Landes Bio-science/Eurekah.com, 2004

Cotter AM, Molloy AM, Scott JM, Daly SF. Elevated plasma homocysteine in early pregnancy: a risk factor for the development of nonsevere preeclamp-sia. Am J Obstet Gynecol 2003;189:391– 4; discussion 4 – 6

116.Mao, D., Che, J., Li, K., Han, S., Yue, Q., Zhu, L., Zhang, W. and Li, L. (2009) Association of homocysteine, asym-metric dimethylarginine, and nitric oxide with pree-clampsia. *Archives of Gynecology and Obstetrics*, 1234-1236.

117.De Falco, M., Pollio, F., Scaramelino, M., Portillo, M. and Lieto, A.D. (2000) Homocysteinemia during preg-nancy and placental disease. *Clinical & Experimental Obstetrics & Gynecology*, **27**, 188-190.

118.Hogg, ChD., Harirah, H., Basherra, H. and Mor, A.G. (2001) Serum soluble fas levels in preeclampsia. Obstet-rics and Gynecology, **97**, 530-532. doi:10.1016/S0029-7844(00)01227-8

119.Lindblad, B., Zaman, S., Malik, A., Martin, H., Ekström, A.M., Amu, S., Holmgren, A. and Norman, M. (2005) Folate, vitamin B12 and homocysteine levels in South Asian women with growth-retarded fetuses. *Acta Obstet-ricia et Gynecologica Scandinavica*, **84**, 1055-1061.

MASTER CHART

S NO	NAME	AGE	IP NO	ABORTION	LMP	EDD	HOMOCYSTEINE	FOLIC ACID
1	Mrs.shyamala	20	18193	G2A1	21/04/15	28/01/16	22.9	4.1
2	Mrs.vinodha	23	19312	G3P1A2	28/02/15	07/12/15	8.6	7.2
3	Mrs.Radha	27	20341	G3P1A1	03/03/15	10/12/15	5.3	11.2
4	Mrs.Pinky	24	21333	G4P1A2	05/04/15	12/01/16	23.5	6
5	Mrs.Rinomary	27	20001	G5P2A3	27/04/15	04/01/16	11.9	12.3
6	Mrs.Gowri	23	18333	G6L1A4	10/04/15	17/01/16	32.1	4.2
7	Mrs.Lakshmi	22	18111	G4P1A2	07/04/15	14/01/16	20.2	5.3
8	Mrs.Gayathri	20	19771	G3L1A1	08/02/15	15/11/15	9.1	14.6
9	Mrs.Abinaya	24	18833	G5A4	15/02/15	22/11/15	8.8	10.3
1	Mrs.Durdana	25	18343	G3A1	17/05/15	24/02/16	7.3	15.2
1	Mrs.Bavani	30	22114	G4L1A2	01/06/15	08/03/16	9.3	16.2
1	Mrs.Mythra	33	23221	G3P1A1	03/02/15	10/01/15	9.1	8.9
1	Mrs.Ragavi	29	24233	G4P1A2	19/04/15	26/01/16	13.3	12.3
1	Mrs.Parveen	27	26112	G5A4	01/05/15	08/02/16	16	4.5
1	Mrs.Pavithra	30	22111	G6P2A4	10/05/15	17/02/16	31.8	3.5

1	Mrs.Saranya	22	19771	G5P1A3	28/04/15	05/02/16	10.1	16.2
1	Mrs.Keerthana	28	15431	G6P2L1A2	26/04/15	03/02/16	6.8	18.2
1	Mrs.Kavya	26	12309	G7P2L1A4	18/04/15	25/01/15	34.5	3.14
1	Mrs.Karthiga	35	32423	G5A3	04/03/15	11/12/15	12.6	19.2
2	Mrs.Halima	26	17834	G6P2L2A4	15/01/15	22/10/15	4.9	15.3
2	Mrs.Vasantha	28	12345	G3P1A2	01/02/15	08/11/15	8.4	13.3
2	Mrs.Muniyammal	20	11231	G4P1L1A1	21/01/15	28/10/15	6.3	12.09
2	Mrs.Mahimaimary	24	15234	G2A1	03/03/15	10/12/15	3.6	12.5
2	Mrs.Baby	20	18122	G4P1A2	08/01/15	15/10/15	13.8	15.5
2	Mrs.Allirani	28	18001	G4P1A4	16/01/15	23/10/15	6.5	16.2
2	Mrs.Mahweswari	32	16444	G5P2L1A3	22/01/15	28/10/15	7.6	10.3
2	Mrs.Vani	25	16577	G6P1A3	26/02/15	05/12/15	11.9	17.9
2	Mrs.Ramya	32	15431	G4A3	17/02/15	24/11/15	7.4	14.9
2	Mrs.Naomi	40	14365	G3P1A1	21/03/15	28/12/15	5.3	12.8
3	Mrs.Kameswari	27	11232	G3P1A2	03/01/15	10/10/15	11.6	7.8
3	Mrs.Ramani	26	13670	G4A3	07/02/15	14/11/15	26.1	3.54
3	Mrs.Janaki	22	18141	G3A2	28/01/15	05/11/15	7.5	13.56

3	Mrs.Revathy	25	17494	G4P1L1A2	09/02/15	16/11/15	6.9	15.14
3	Mrs.Jeyanthi	29	16577	G5A3	15/01/15	22/10/15	4.7	16.3
3	Mrs.Mary	23	21356	G6P2L1A3	10/02/15	17/11/15	12.5	18.5
3	Mrs.Latha	21	23415	G4A2	05/03/15	12/12/15	10.4	19.21
3	Mrs.Muthammal	24	18345	G3P1A1	12/12/14	19/09/15	11.5	10.34
3	Mrs.SelvI	36	26445	G5A4	27/12/14	03/09/15	8.9	9.47
3	Mrs.Radhika	38	22111	G6P1L1A3	01/12/14	08/09/15	6.2	16.23
4	Mrs.Anitha	29	24232	G5A4	08/12/14	15/09/15	35.9	5.2
4	Mrs.Ramya	27	20003	G3P1A1	10/01/15	17/10/15	10.4	19.9
4	Mrs.Nithya	25	20112	G3A1	31/01/15	07/10/15	9.5	11.8
4	Mrs.suseela	24	17256	G4P1A2	28/02/15	07/11/15	10.5	19.1
4	Mrs.Tamilmalar	28	32849	G5P2L1A2	04/04/15	11/01/16	11.5	16.6
4	Mrs.Reshma	28	19837	G4L0A4	26/04/15	02/02/16	26.3	6.1
4	Mrs.Nisha	20	23840	G6P2L1A2	11/04/15	18/12/15	8.5	15.6
4	Mrs.jahabart	35	23423	G5A3	28/03/15	04/12/15	7.1	14.8
4	Mrs.Nivedha	30	23188	G3P2A1	16/03/15	23/12/15	11.5	18.3
4	Mrs.Shanthi	25	14465	G4P1L1A2	11/01/15	18/10/15	9.1	19.6

5	Mrs.Vinodhini	22	13324	G2P1A1	01/02/15	08/11/15	7.9	12.9
5	Mrs.shalini	21	18234	G4P1A3	30/04/15	07/02/15	10.5	15.5
5	Mrs.Vathsala	31	21342	G4A2	02/02/15	09/11/15	32.4	4.8
5	Mrs.Sheela	29	21132	G5P1L1A2	01/04/15	08/01/15	6.12	15.15
5	Mrs.Gomathi	17	15345	G3P1A1	02/12/15	09/11/15	5.9	10.1
5	Mrs.Nishanthini	24	19232	G5A4	03/05/15	10/02/16	13.7	9.9
5	Mrs.Devi	25	21345	G2A1	10/05/15	17/02/16	9.2	16.3
5	Mrs.Ragavi	22	27774	G2A1	15/05/15	22/02/16	8.45	14.56
5	Mrs.Nivedhitha	29	22281	G3A3	01/03/15	08/12/15	14	9.12
5	Mrs.Surya	28	22243	G6P2L2A4	15/02/15	22/11/15	33.51	5.9
6	Mrs.Kala	23	28736	G5P1L1A2	17/01/15	24/10/15	8.4	19.6
6	Mrs.Chandra	26	21129	G6P1L1A3	21/01/15	28/10/15	7.3	11.7
6	Mrs.Sulekha	27	22134	G3A2	07/02/15	14/11/15	11.7	8.9
6	Mrs.Lekha	22	13245	G3P1A2	09/04/15	16/01/16	7.7	7.9
6	Mrs.Sulochana	29	21111	G6P2A4	14/03/15	21/12/15	6.1	15.3
6	Mrs.Shamili	26	54388	G3A2	20/02/15	27/11/16	8.78	17.4
6	Mrs.Anjali	25	67234	G2A1	11/05/15	18/02/16	5.17	18.3

6	Mrs.Baby		31	72226	G5P1A4	15/04/15	22/01/16	37.8	4.9
6	Mrs.Navya		24	47388	G3P1A2	11/03/15	18/12/15	5.77	14.4
6	Mrs.Nirosha		26	38844	G3P1L1A1	10/05/15	17/02/16	7.88	13.6
7	Mrs.Basumathi		32	21345	G2A1	22/04/15	29/01/16	12.6	9.15
7	Mrs.Uma		25	54761	G5P1A4	07/05/15	14/02/16	13.7	10.6
7	Mrs.Thirupatham		22	36452	G4A3	10/05/15	17/02/16	10.4	8.9
7	Mrs.Manimegalai		31	32465	G5P1A2	03/06/15	10/03/16	8.3	17.3
7	Mrs.Joycy		19	35546	G3A1	07/01/15	14/10/15	16.78	6
7	Mrs.Rosy		26	62803	G2A1	21/02/15	28/11/15	7.1	16.8
7	Mrs.Kavitha		25	88801	G3P1A2	04/03/15	11/12/15	5.4	17.2
7	Mrs.Raasi		32	37465	G5P1A3	14/02/15	21/11/15	9.2	19.4
7	Mrs.Farhana		27	30002	G6 P1A3	05/01/15	12/10/15	30.9	3.25
7	Mrs.Sowmi		21	32103	G2 P1A1	16/02/15	22/11/15	8.6	12.6
8	Mrs.Ranjini		22	27738	G4P1A3	21/04/15	28/01/16	7.4	14.5
8	Mrs.aAnnejoseph		25	33390	G4P0L0A4	22/03/15	29/12/15	9.8	13.9
8	Mrs.Richaa		27	11322	G3P1A2	26/02/15	05/12/15	12.3	11.2
8	Mrs.Parveen		33	32211	G4P1A3	23/02/15	30/11/15	14.1	9.4

8	Mrs.Vinodhini	30	21111	G5P1A4	02/01/15	09/10/15	24.7	3.9
8	Mrs.Girija	35	23111	G6P2A4	15/03/15	21/12/15	13.2	15.6
8	Mrs.Fathima	32	12903	G3P1A1	22/04/15	29/01/16	8.8	17.3
8	Mrs.Chandralekha	21	21309	G4A2	03/01/15	10/10/15	18.54	3.5
8	Mrs.Umarani	25	21113	G3P1A1	15/01/15	21/10/15	10.6	19.1
8	Mrs.Praveena	27	20999	G4A3	08/04/15	15/01/16	6.7	16.7
9	Mrs.Gheetha	28	24551	G5P1A4	04/03/15	11/10/15	20.9	4.4
9	Mrs.Priya	30	21113	G6P2A3	04/02/15	11/09/15	27.3	5.3
9	Mrs.Keerthi	29	17677	G3P1A2	28/02/15	07/12/15	23.45	3.8
9	Mrs.Ramya	21	22200	G5P1A3	03/03/15	10/12/15	9.1	13.7
9	Mrs.Ashwini	22	27777	G3P1A2	21/02/15	28/09/15	6.8	14.3
9	Mrs.Nikhitha	26	22344	G4P1A2	17/02/15	24/09/15	18.2	5.6
9	Mrs.Jessica	28	12367	G5P1A3	04/02/15	11/11/15	11.9	9.7
9	Mrs.Sharon	26	16565	G3A2	03/03/15	12/12/15	10.7	14.1
9	Mrs.Selvambal	35	22222	G7P1A5	05/04/15	12/01/16	102.2	2.1
9	Mrs.Elakkiya	24	14433	G3A2	20/05/15	27/02/16	17.84	4.6
1	Mrs. Pushpa latha	28	28939	G5P1A3	26/03/15	03/01/16	23.4	4.2

VALUES OF CONTROL

S NO	NAME	AGE	IP NO	OBSTETRIC code	LMP	EDD	GESTATIONAL AGE	HOMOSY STEINE	FOLIC ACID
1.	Mrs mala	20	11305	G3P2L2	10/02/15	17/11/15	11 WEEKS 2 DAYS	6.8	15.1
2.	mrs amutha	22	15623	G2P1L1	05/03/15	12/12/15	10 WEEKS 2 DAYS	12	8.1
3.	mrs sangeetha	24	23343	G2P1L1	12/12/14	19/09/15	12 WEEKS 2 DAYS	11.1	16.6
4.	mrs aseena	26	12324	G2P1L1	27/12/14	03/09/15	13 WEEKS 1 DAYS	13.4	8.9
5.	mrs shoba	28	22414	G2P1L1	01/12/14	08/09/15	11 WEEKS 3 DAYS	10.3	7.8
6.	mrsvijaya	32	23412	G2P1L1	08/12/14	15/09/15	12 WEEKS 2 DAYS	8.6	16.1
7.	mrs savitha	23	34520	G3P2L2	10/01/15	17/10/15	10 WEEKS 4 DAYS	6.2	17.3
8.	mrs sumathi	26	21421	G2P1L1	31/01/15	07/10/15	11 WEEKS 6 DAYS	8.9	14.5
9.	mrs usha	27	12333	G2P1L1	28/02/15	07/11/15	13 WEEKS 3 DAYS	12.3	16.6
10.	mrs lekshmi	30	12311	G2P1L1	04/04/15	11/01/16	10 WEEKS 4 DAYS	14.3	8.9
11.	mrs malliga	19	19322	G2P1L1	26/04/15	02/02/16	12 WEEKS 2 DAYS	14.9	10.1
12.	mrs devi	24	11311	G2P1L1	11/04/15	18/12/15	12 WEEKS 6 DAYS	10.3	14.5
13.	mrs selvi	29	12221	G2P1L1	28/03/15	04/12/15	13 WEEKS 1 DAY	9.6	15.3
14.	mrs renu	30	15311	G2P1L1	16/03/15	23/12/15	11 WEEKS 4 DAYS	8.3	17.3
15.	mrs usha	35	11911	G3P2L2	11/01/15	18/10/15	11 WEEKS 2 DAYS	7.6	18.5
16.	mrs kalaivani	32	12222	G2P1L1	01/02/15	08/11/15	10 WEEKS 1 DAY	6.9	19.1
17.	mrs nirmala	26	17000	G2P1L1	30/04/15	07/02/15	13 WEEKS 3 DAYS	12.3	10.1
18.	mrs anjali	22	10011	G2P1L1	02/02/15	09/11/15	11 WEEKS 2 DAYS	13.5	16.9
19.	mrs roshima	20	11818	G2P1L1	01/04/15	08/01/15	12 WEEKS 5 DAYS	14.1	19.3
20.	mrs thulasi	19	18888	G2P1L1	02/12/15	09/11/15	13 WEEKS	9.1	19.6
21.	mrs janey	24	19119	G3P2L2	03/05/15	10/02/16	12 WEEKS 3DAYS	13.2	10.1
22.	mrs rizwana	30	18111	G2P1L1	10/05/15	17/02/16	10 WEEKS 4 DAYS	6.1	16.1
23.	mrs jeyashree	22	11231	G2P1L1	15/05/15	22/02/16	12 WEEKS 2 DAYS	7.9	17.3
24.	mrs devi	26	12222	G2P1L1	01/03/15	08/12/15	11 WEEKS 4 DAYS	7.6	9.6
25.	mrs divya	23	14333	G2P1L1	15/02/15	22/11/15	13 WEEKS 1 DAY	8.5	10.3
26.	mrs soumya	19	22125	G2P1L1	21/04/15	28/01/16	12 WEEKS 2 DAYS	11.2	11.2
27.	mrs parveen	24	21122	G2P1L1	28/02/15	07/12/15	12 WEEKS 2 DAYS	6.9	13.3
28.	mrs sujatha	26	24211	G2P1L1	03/03/15	10/12/15	11 WEEKS	14.6	14.5
29.	mrs geethmala	32	26122	G3P2L2	05/04/15	12/01/16	11 WEEKS 3 DAYS	10.6	16.7
30.	mrs arun	35	20011	G2P1L1	27/04/15	04/01/16	12 WEEKS 1DAY	8.9	19.8
31.	mrs meena	20	24112	G2P1L1	10/04/15	17/01/16	10 WEEKS 5 DAYS	12.3	10.8
32.	mrs sarala	29	25222	G2P1L1	07/04/15	14/01/16	13 WEEKS 2 DAYS	8.6	8.3
33.	mrs kalaivani	27	16589	G2P1L1	08/02/15	15/11/15	11 WEEKS 4 DAYS	13.4	7.6
34.	mrs logeshwari	19	21214	G2P1L1	15/02/15	22/11/15	12 WEEKS 5 DAYS	14.1	9.8
35.	mrs elayaveni	18	11222	G2P1L1	22/03/15	29/12/15	13 WEEKS 2 DAYS	10.3	10.3
36.	mrs vani	26	18121	G2P1L1	26/02/15	05/12/15	10 WEEKS 4 DAYS	8.9	14.6
37.	mrs anjali	34	28112	G3 P2L2	23/02/15	30/11/15	10 WEEKS 2 DAYS	13.2	13.2
38.	mrs poomethi	36	27112	G2P1L1	02/01/15	09/10/15	12 WEEKS 6 DAYS	13.9	12.9
39.	mrs booshan	26	21122	G2P1L1	15/03/15	21/12/15	11 WEEKS 3 DAYS	10.7	8.9
40.	mrs lakshaya	22	26112	G3P2L2	22/04/15	29/01/16	11 WEEKS 4 DAYS	12.7	16.6
41.	mrs lochini	20	27722	G2P1L1	03/01/15	10/10/15	11 WEEKS 2 DAYS	11.2	17.8
42.	mrs srimethi	29	21221	G2P1L1	15/01/15	21/10/15	10 WEEKS 2 DAYS	8.1	10.3
43.	mrs tamilvani	27	24112	G2P1L1	08/04/15	15/01/16	12 WEEKS 2 DAYS	11.9	16.6
44.	mrs beena	32	29112	G2P1L1	04/03/15	11/10/15	13 WEEKS 1 DAYS	7.3	12.3
45.	mrs priyamani	26	30111	G2P1L1	04/02/15	11/09/15	13 WEEKS 1 DAY	14.2	9.6
46.	mrs shobana	27	14531	G2P1L1	28/02/15	07/12/15	12 WEEKS 4 DAYS	9.6	10.3
47.	mrs baseena	23	13530	G2P1L1	03/03/15	10/12/15	13 WEEKS 1 DAY	8.6	16.7
48.	mrs nivedhana	24	15222	G3P2L2	21/02/15	28/09/15	11 WEEKS 4 DAYS	10.3	15.8
49.	mrs thara	20	15555	G2P1L1	17/02/15	24/09/15	11 WEEKS 2 DAYS	4.7	10.7
50.	mrs sultana	32	23112	G2P1L1	04/02/15	11/11/15	10 WEEKS 1 DAY	11.2	19.6

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51.	mrs manimalai	23	25122	G2P1L1	03/03/15	12/12/15	13 WEEKS 3 DAYS	8.3	9.9
52.	mrs niveditha	28	27188	G2P1L1	05/04/15	12/01/16	11 WEEKS 2 DAYS	9.6	12.9
53.	mrs sunitha	25	11001	G2P1L1	20/05/15	27/02/16	12 WEEKS 5 DAYS	13.1	13.6
54.	mrs devishree	19	14361	G2P1L1	26/03/15	03/01/16	13 WEEKS	12.9	15.8
55.	mrs kavitha	18	18111	G2P1L1	17/05/15	24/02/16	12 WEEKS 3DAYS	14.3	7.9
56.	mrs renu	26	14322		01/06/15	08/03/16	10 WEEKS 4 DAYS	9.6	19.1
57.	mrs vinitha	21	21112	G3P2L2	03/02/15	10/01/15	12 WEEKS	8.6	11.3
58.	mrs vedha	27	28111	G2P1L1	19/04/15	26/01/16	13 WEEKS 4 DAYS	8.5	13.9
59.	mrs bhavani	22	25333	G2P1L1	01/05/15	08/02/16	10 WEEKS 5 DAYS	7.8	11.6
60.	mrs poongodi	30	23331	G2P1L1	10/05/15	17/02/16	13 WEEKS 2 DAYS	6.9	8.7
61.	mrs seema	26	24442	G2P1L1	28/04/15	05/02/16	11 WEEKS 4 DAYS	10.3	9.1
62.	mrs kani	23	28112	G2P1L1	26/04/15	03/02/16	12 WEEKS 5 DAYS	12.1	15.1
63.	mrs aseena	24	14322	G2P1L1	18/04/15	25/01/15	13 WEEKS 2 DAYS	7.8	8.1
64.	mrs tamilarasi	27	15322	G2P1L1	04/03/15	11/12/15	10 WEEKS 4 DAYS	7.5	16.6
65.	mrs soundarya	32	14333	G2P1L1	15/01/15	22/10/15	10 WEEKS 2 DAYS	13.5	8.9
66.	mrs datchayani	26	15322	G2P1L1	01/02/15	08/11/15	11 WEEKS 6 DAYS	13.3	7.8
67.	mrs renuga	27	14333	G2P1L1	21/01/15	28/10/15	13 WEEKS 3 DAYS	9.6	16.1
68.	mrs jayashree	29	17311	G2P1L1	03/03/15	10/12/15	10 WEEKS 4 DAYS	14.1	17.3
69.	mrs amala	25	18222	G2P1L1	08/01/15	15/10/15	12 WEEKS 2 DAYS	8.9	14.5
70.	mrs meenakshi	28	21333	G3P2L2	16/01/15	23/10/15	12 WEEKS 6 DAYS	7.6	16.6
71.	mrs mina	24	11231	G2P1L1	22/01/15	28/10/15	13 WEEKS 1 DAY	8.9	14.3
72.	mrs mekala	22	14311	G2P1L1	26/02/15	05/12/15	11 WEEKS 4 DAYS	8.7	10.1
73.	mrs ananditha	28	19881	G2P1L1	17/02/15	24/11/15	11 WEEKS 2 DAYS	6.9	14.5
74.	mrs kalaivani	30	20002	G2P1L1	21/03/15	28/12/15	10 WEEKS 1 DAY	9.3	15.3
75.	mrs preethi	23	23331	G2P1L1	03/01/15	10/10/15	13 WEEKS 3 DAYS	10.6	17.3
76.	mrs amritha	27	29911	G2P1L1	07/02/15	14/11/15	11 WEEKS 2 DAYS	12.3	18.5
77.	mrs ringu devi	22	27722	G2P1L1	28/01/15	05/11/15	12 WEEKS 5 DAYS	6.9	19.1
78.	mrs malliga	32	21122	G3P2L2	09/02/15	16/11/15	10 WEEKS 5 DAYS	7.8	10.1
79.	mrs reena	35	14333	G2P1L1	15/01/15	22/10/15	13 WEEKS 2 DAYS	10.1	16.9
80.	mrs reeta devi	26	30011	G2P1L1	10/02/15	17/11/15	11 WEEKS 4 DAYS	4.3	19.3
81.	mrs dinakavi	28	27112	G2P1L1	05/03/15	12/12/15	12 WEEKS 5 DAYS	6.6	19.6
82.	mrs usha	26	28221	G2P1L1	12/12/14	19/09/15	13 WEEKS 2 DAYS	10.1	16.14
83.	mrs nirmala	22	22333	G2P1L1	27/12/14	03/09/15	10 WEEKS 4 DAYS	12.9	16.1
84.	mrs priyamani	29	21112	G2P1L1	01/12/14	08/09/15	10 WEEKS 2 DAYS	8.9	17.3
85.	mrs banu	25	18881	G2P1L1	08/12/14	15/09/15	11 WEEKS 5 DAYS	9.6	17.8
86.	mrs thulasi	32	21122	G2P1L1	10/01/15	17/10/15	10 WEEKS 6 DAYS	10.6	10.3
87.	mrs likitha	23	28877	G2P1L1	31/01/15	07/10/15	12 WEEKS 2 DAYS	12.9	11.2
88.	mrs sivalochini	26	27112	G2P1L1	28/02/15	07/11/15	13 WEEKS	12.3	13.3
89.	mrs preetha	20	30221	G3P2L2	04/04/15	11/01/16	13 WEEKS 1 DAY	10.2	14.5
90.	mrs sumathi	23	22233	G3P2L2	26/04/15	02/02/16	11 WEEKS 4 DAYS	7.3	16.7
91.	mrs devika	28	27711	G2P1L1	11/04/15	18/12/15	11 WEEKS 2 DAYS	9.8	19.8
92.	mrs sangeetha	23	28833	G2P1L1	28/03/15	04/12/15	10 WEEKS 1 DAY	14.1	10.8
93.	mrs amritha	21	29911	G2P1L1	16/03/15	23/12/15	13 WEEKS 3 DAYS	6.2	8.3
94.	mrs shobana	26	31122	G2P1L1	11/01/15	18/10/15	11 WEEKS 2 DAYS	7.8	19.3
95.	mrs sumathy	22	28221	G2P1L1	01/02/15	08/11/15	12 WEEKS 5 DAYS	10.1	15.2233
96.	mrs deepa	27	27112	G2P1L1	30/04/15	07/02/15	13 WEEKS	13.3	16.8
97.	mrs jayashree	33	22456	G2P1L1	02/02/15	09/11/15	12 WEEKS 3DAYS	8.3	18.3
98.	mrs ramya	26	11568	G2P1L1	01/04/15	08/01/16	10 WEEKS 4 DAYS	9.6	17.8
99.	mrs keerthi	27	19568	G2P1L1	02/12/15	09/09/16	12 WEEKS 3 DAYS	14.5	10.1
100	Mrs. priya	22	25684	G2P1L1	23/09/15	30/06/16	11 WEEKS 2 DAYS	12.3	9.9

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ABBREVIATION

RPL - Recurrent Pregnancy Loss

HHCH - Hyperhomocysteinemia

NTD - Neutral tube Defect

RM - Recurrent Miscarriage

PCOS - Polycystic Ovarian Syndrome

A PAS - Antiphospholipid antibody syndrome

MTHFR - Methylene tetrahydro folate Reductase

LAC - Lupus Anticoagulant

TLC - Tender Loving Care

HCG - Human Chronic Gonadotrophin

SD - Standard Deviation

IUD - Intra Utrine Death

TC - Transcobalamin

PROFORMA

NAME

AGE

IP/OP NO

ADDRESS

TELEPHONE NO

MENSTURAL H/O

• MENARCHY

• CYCLES REGULAR/IRREGULAR

• DURATION

• LMP

MARITAL H/O

• AGE AT MARRIAGE

• CONSAGNUITY

OBSTETRIC H/O

• YEARS AFTER MARRIAGE

• NATURAL/ASSISTED

• ANTENATAL PERIOD

• 1ST TRIMESTER

• 2ND TRIMESTER

• 3RD TRIMESTER

• PEDIGREE

• PERI CONCEPTIONAL EXPOSURE

• ILLNESS(FEVER,JAUNDICE)

• MEDICATION

• EXPOSURE

FAMILY H/O

• ABORTION,INFERTILITY,BIRTH

• DEFECTS,MENTAL RETARDATION

RESIDENCE H/O

• (FACTORY,TANNERY,POLLUTED

• WATER,RADIATION,BURNING)

• OCCUPATION H/O

GENERAL EXAMINATION

• WIFE HUSBAND

• VITALS

• OBSTETRIC EXAMINATION

INVESTIGATIONS

• Hb

• BLOOD UREA

• BLOOD SUGAR

• SERUM CREATINE

• HIV/VDRL

- HbSAg
- CERVICAL SWAB
- HOMOCYSTEINE
- USG
- LFT

CONSENT FORM

I agree to participate in the study entitled "**EVALUATION OF HOMOCYSTEINE & FOLIC ACID LEVELS IN PREGNANCY LOSS**".

I confirm that I have been told about this study in my mother tongue and have had the opportunity to clarify my doubts.

I understand that my participation is voluntary and I may refuse to participate at any time without giving any reasons and without affecting my benefits.

I agree not to restrict the use of any data or results that arise from this study.

Name of the participant :

Sign / Thumb print:

Sign of Investigator :

தகவல் படிவம்

ஸ்டான்லி மருத்துவமனையின் ஆர்.எஸ்.ஆர்.எம். மருத்துவமனையில் மகப்பேறு மற்றும் பெண்கள் நல மருத்துவமனையில் மேற்கொள்ளப்படும் ஆய்வு தொடர்பான தகவல் படிவம் இது. இந்த ஆய்வு மரு. டாக்டர். என்.ஐ.சௌகந்திகா அவர்களால் மற்றும் பிற அனுபவம் வாய்ந்த மருத்துவர்களின் உதவியோடு நடத்தப்படுகிறது.

இந்த ஆய்வு கருச்சிதைவு ஏற்பட்டுள்ள தய்மார்களுக்கு ஹோமோசிஸ்டின் (Homocysteine) மற்றும் போலிக் ஆசிடின் (Folic Acid) அளவினை கண்டரறிந்து மதிப்பிடுதல் தொடர்பான ஆய்வினை மேற்கொள்ளுதல்.

இந்த ஆய்வில் உட்படுத்தப்படும் பெண்களுக்கு எந்த பாதிப்பும் இல்லை என்பதை தெரிவித்துக்கொள்கிறேன். இந்த ஆய்வு தங்கள் சுயவிருப்பத்துடன் முன்வந்தால் மட்டுமே மேற்கொள்ளப்படும்.

ஒப்புதல் படிவம்

திருமதி _____

_____

_____

_____

என்ற விலாசத்தில் வசிக்கும் நான் எனக்கு அளிக்கப்பட்ட தகவல் படிவத்தில் உள்ள விவரங்களையும் படித்தும் கேட்டும் புரிந்து கொண்டேன்.

இந்த ஆய்விற்கு தேவையான இரத்தத்தை ஊசி மூலம் எடுத்துகொள்ள சம்மதிக்கிறேன்.

ஆய்வின் முடிவுகளை சொந்த அடையாளங்களை வெளியிடாமல் மருத்துவ ஆராய்ச்சிக்காக பயன்படுத்தி கொள்ள சம்மதிக்கிறேன்.

நாள்: **கையொப்பம்**

இடம்: **பெயர்**

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Filesize 760.71K

Pagecount 79

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Charactercount 33,223

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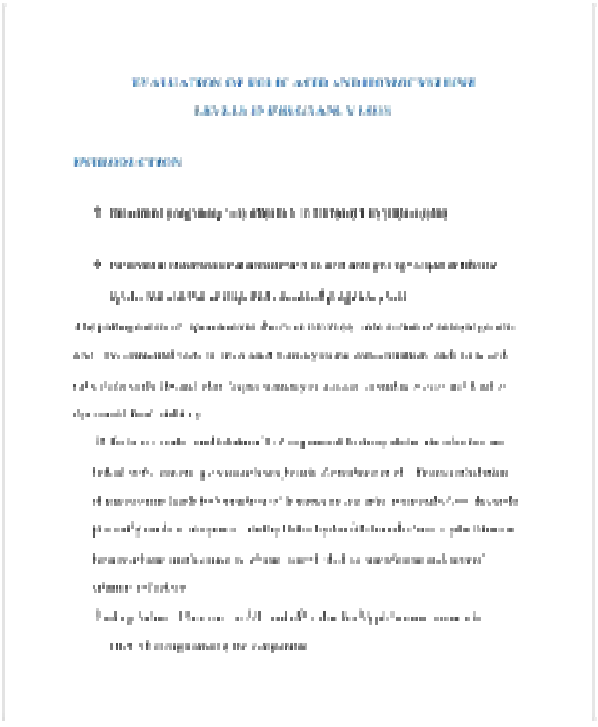

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INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Evaluation of Homocysteine & Folic Acid levels in Pregnancy loss.

Principal Investigator : Dr Sowganthika.N.I

Designation : PG MS (O & G)

Department : Department of O & G
Stanley Medical College
Chennai -01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 10.06.2015 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.